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A.N.M. Alamgir

Therapeutic Use of Medicinal Plants and Their Extracts: Volume 1

Pharmacognosy

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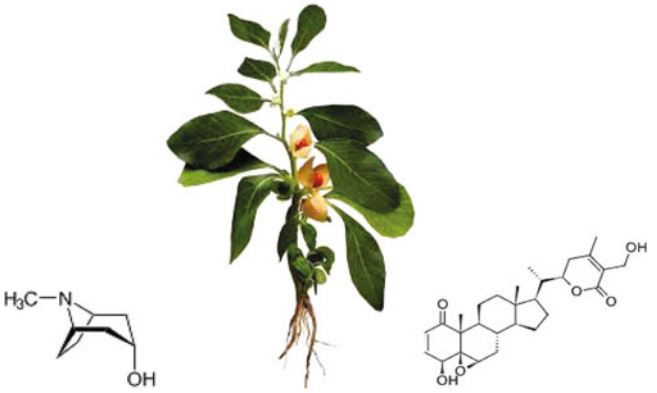
Therapeutic Use of Medicinal Plants and Their Extracts: Volume 1

Pharmacognosy

(Botany, pharmacology, therapy, culture and commerce of medicinal herbs)

For B. Sc. and M. Sc. Students



Tropane alkaloid - Tropine, *Withania somnifera*, Steroidal lactone - Withaferin A

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Dedicated to the memory of my beloved parents

Contents

Abbreviations

2,4,5-T	2,4,5-trichlorophenoxyacetic acid
2,4-D	Dichlorophenoxy acetic acid
4 CPA	4-chlorophenoxyacetic acid
5-MeO-DMT	5-methoxy-N,N-dimethyltryptamine, buffotoxin
AAS	Atomic absorption spectrophotometer
ABA	Abscisic acid
AC	Activated charcoal
AD	Anno domini
ADA	Adenosine deaminase
ADP	Adenosine diphosphate
AHAs	Alpha hydroxy acids
AHP	American herbal pharmacopoeia
AIDS	Acquired immunodeficiency syndrome
ALA	Alpha-lipoic acid
AMP	Adenosine monophosphate
ANF	American National Formulary
ANS	Autonomic nervous system
AP	African pharmacopoeia
API/APP	Active pharmaceutical ingredient/product
ATC	Anatomical therapeutic chemical
ATP	Adenosine triphosphate
BA	6-benzyladenine
BAP	6-benzylaminopurine
BC	Before Christ
BCG	Bacillus calmette-guerin
BDNF	Bangladesh national formulary
BHC	Benzene hexachloride
BNF	British National Formulary
BOL	Barcode of Life
BoNT	Botulinum neurotoxins

BP	British pharmacopoeia
BPC	British pharmaceutical codex
BSS	Balanced salt solutions
BTC	Behind-the-counter
C3/C4 pathway	Calvin-Basham (3 carbon acid) pathway / HatchSlack (4 carbon acid) pathway of CO2 assimilation
CA	Conservation agriculture
CAD	Charged aerosol detector
CAMs	Complementary and alternative medicines
CBD	Convention on biological diversity
CBOL	Consortium for the barcode of life
CCD	Charge-coupled device
CCEE	Countries of Central and Eastern Europe
CCK	Cholecystokinin
CE	Capillary electrophoresis
CE-DAD	Capillary electrophoresis with diode array detector
CF	Cystic fibrosis
CHD	Coronary heart disease
CIPIH	Commission on intellectual property rights, innovation and public health
CLA	Conjugated linoleic acid
CML	Cordyceps militaris lectin
CNS	Central nervous system
COMT	Catechol-o-methyltransferase
COMTRADE	Common format for transient data exchange
COX-1/2	Cyclooxygenase-1/2
CSIR	Council of scientific and industrial research
CTD	Common Technical Document
CTM	Chinese traditional medicine
CUOXAM	Ammoniacal solution of copper oxide
CZE	Capillary zone electrophoresis
DAD	Diode array detector
DDT	Dichlorodiphenyltrichloroethane
delta-9-THC	delta-9-tetrahydrocannabinol
DIM	Diindolylmethane
DMEM	Dulbecco's Modified Eagle's Medium
DMSO	Dimethyl sulfoxide
DMT	Dimethyltryptamine
DNA	Deoxy ribonucleic acid
DO	Doctor of osteopathy
DSHEA	Dietary Supplement Health and Education Act
ECM	Extra cellular matrix
ED	Erectile dysfunction
EDQM	European Directorate for the Quality of Medicines
EDTA	Ethylenediaminetetraacetic acid

EGCG	Epigallocatechin-3-gallate agency
ELISA	Enzyme-linked immunosorbent assay
ELSD	Electric light scattering detector
EMA	European medicines agency
EMEA	European medicines evaluation agency
EMEM	Eagle's Minimum Essential Medium
ENT	Ear, nose, and throat
ER	Endoplasmic reticulum
ESCOP	European Scientific Cooperative on Phytotherapy
EU	European union
FAO	Food and agriculture organization
FDA	Federal food and drug administration
FDCA	Federal food, drug, and cosmetics act
FID	Flame ionization detector
FOSHU	Foods for specified health uses
FYM	Farmyard manure
GA3	Gibberellic acid
GABBA	Gamma-aminobutyric acid A
GACP	Good agricultural and collection practice
GACPs	Good agricultural and collection practices
GC	Gas chromatography
GC-MS	Gas chromatography mass mapectrophotometry
GI	Gastrointestinal
GI	Geographical indications
GLC	Gas–liquid chromatography
GLP	Good laboratory practice
GMP	Good manufacturing practice
GnRH	Gonadotrophin-releasing hormone
GP	General practitioner
GPAIP	Good Plant Authentication and Identification Practice
GRs	Genetic resources
HA	Hyaluronic acid
hCG	Human chronic gonadotropin
HCH	Hexachlorocyclohexane
HEPA	High efficiency particle air filter
hGH	Human growth hormone
HILIC	Hydrophilic interaction chromatography
HIV	Human immunodeficiency virus
HMPC	Committee on herbal medicinal products
HMPC	Herbal medicinal products
HPLC	High-performance liquid chromatography
HPLC-DAD	HPLC coupled to diode-array detection
HPLC-ELSD	HPLC-evaporative light scattering detector
HPTLC	High-performance TLC
HR-MS	High-resolution mass spectrometry

HRs	Hairy roots
HSCCC	High-speed counter-current chromatography
HTS	High-throughput screening
HYV	High yielding variety
I3C	Indole-3-carbinol
IAA	Indole-3 acetic acid
IBA	Indole butyric acid
ICDRA	International conference of drug regulatory authorities
ICN	International code of nomenclature
ICP	Inductively coupled plasma
ICP-OES	Inductively coupled plasma-optical emission spectrometry
IDO	Indoleamine 2,3-dioxygenase
IGC	Intergovernmental Committee
IgE	Immunoglobulin E
IP	Indian pharmacopoeia
IP	Intellectual property
IPR	Intellectual property right
IR	Infrared
IRS	Infrared spectroscopy
IUCN	International union for conservation of nature
ITS	International transcribed spacer
JKMA	Japan Kampo Medicines Manufacturer Association
kD	Kilo dalton
KTTKS	Collagen pentapeptide: Lys-Thr-Thr-Lys-Ser
LC	Liquid chromatography
LC-MS	Liquid chromatography coupled to mass spectrometry
L-DOPA	Levodopa or L-3,4-dihydroxyphenylalanine
LHRH	Luteinizing hormone-releasing hormone
LOD	Loss on drying
LS	Longitudinal section
LSD	Lysergic acid diethylamide
MAO	Monoamine oxidase
MAOIs	Monoamine oxidase inhibitors
matK	Maturase K, a plant plastidial gene
MC	Moisture content
MCf	Maximum final moisture content
MD	Medical doctor
MEM	Minimum essential medium
MECC	Micellar electronic capillary chromatography
MEKC	Micellar electrokinetic chromatography
MEP pathway	Methyl D-erythritol 4-phosphate pathway/non-mevalonate pathway
MHRA	Medicines and healthcare products regulatory agency
MIR	Mid-infrared

MJ	Methyl jasmonate
MPAs	medicinal and aromatic plants
MPs	Medicinal plants
MPS I	Mucopolysaccharidosis type I
MS	Mass spectrometry
MS medium	Murashige and Skoog medium
Mw	Mass of water
NA	Numerical aperture
NAA	Neutron activation analysis
NAA	Naphthaleneacetic acid
NAPRALERT	Natural Medicines Comprehensive Database
NBSB	National Biological Standards Board
NCCAM	National Center for Complementary and Alternative Medicines
NE	Norepinephrine
NF	National formulary
NGA	N-acetyl-glucosamine
NHPD	Natural health products directorate
NIRS	Nearinfrared spectroscopy
NIS	Newly independent states
NMR	Nuclear magnetic resonance
NPK fertilizers	Nitrogen, phosphorus, and potassium fertilizers
NPs	Natural products
NSAIDs	Non-steroidal anti-inflammatory drugs
NTA	Notice to Applicants
omega-3 PUFAs	Omega-3 polyunsaturated fatty acids
MEG-3 brand omega-3 EPA/DHA	Eicosapentaenoic acid/docosahexaenoic acid
OPLC	Over-pressured layer chromatography
OTC	Over-the-counter
PAF	Platelet activity factor
PBS	Phosphate-buffered saline
PCPA	p-chlorophenoxyacetic acid
PEITC	Phenethyl isothiocyanate
PEP	Phosphoenolpyruvate
Ph. Int.	International pharmacopoeia
PIPs	Plant-incorporated protectants
POM	Prescription only medicines
POPs	Persistent organic pollutants
PP2A	Protein phosphatase-2A
PVP	Polyvenyl pyrrolodin
QDG	Quality Drafting Group
QP	Qualified Person
QTLC	Quantitative TLC
R&D	Research and development

Rad-br	Radium bromatum
RBC	Red blood corpuscles
rcbL	Ribulose bisphosphate carboxylase large chain
RECOMBIVAX HB	Recombinant hepatitis B vaccine
Rf	Retention factors or relative to front, determined as distance moved by the compound/distance moved by the solvent
RH	Relative humidity
RIA	Radioimmunoassay
RNA	Ribonucleic acid
RP	Reversed phase
RP-IPC-HPLC	Reversed-phase ion pair chromatography-HPLC
RPMI	Roswell park memorial institute
SA	Salicylic acid
SAX-HPLC	Strong anion exchange-HPLC
SCID	Severe combined immunodeficiency
SEC	Size exclusion chromatography
SH medium	Schenk and Hildebrand medium
SI	Stomatal index
SOD	Superoxide dismutase
SSM	Siddha system of medicine
STN	Scientific and technical network
TBGRI	Tropical Botanic Garden and Research Institute
TCA cycle	Tricarboxylic acid cycle
TCAM	Traditional/complementary and alternative medicine
TCM	Traditional Chinese Medicine
TEM	Transmission electron microscope
T DNA	Transfer DNA
TeNT	Tetanus neurotoxin
THM	Traditional herbal medicine
TK	Traditional knowledge
TKDL	Traditional knowledge digital library
TKRC	Traditional knowledge resource classification
TLC	Thin-layer chromatography
TL DNA	Left T DNA
TMK	Traditional medical knowledge
tPA	Tissue plasminogen activator
TR DNA	Right T DNA
TS	Transverse section
UNCTAD	United Nations Conference on Trade and Development
UNESCO	United Nations Educational, Scientific, and Cultural Organization
US	Ultrasound
USP	United States Pharmacopeia
USPTO	United States Patent and Trademark Office

UV	Ultraviolet
VIDS	Venation Image Database System
wb	Wet basis
WHO	World Health Organization
WIPO	World Intellectual Property Organization
WWF	World Wide Fund for Nature
XRFS	X-ray fluorescence spectroscopy

Chapter 1
Introduction

Abstract Pharmacognosy is the scientific study of crude drug principles of natural origin including their history, collection, preparation, standardization, use, cultivation, and commerce. Herbal preparations from plant, animal, and mineral are medicinal and promote health beyond basic nutrition. Pharmacognosy is a multidisciplinary subject and requires knowledge of botany, ethnobotany, phytochemistry, microbiology, pharmacology, pharmaceutics, etc. Botany and ethnobotany are important for identification, genetics, cultivation, etc. of drug plants; chemical characterization includes isolation, identification, and quantification of drug plant constituents; and pharmacology informs about the biological effects of the crude drugs on cell cultures, animals and humans. The majority of the drugs available in the market today are obtained mostly from natural sources, and about 80% of the world's rural people rely on herbal medicine for primary health care. The renaissance of herbal medicine in the recent years has created an urge for intensive studies in the field of pharmacognosy to ascertain the quality, efficacy, and safety of the herbal products. Medicinal plants are widely used across the world in different traditional systems of medicine including Ayurveda, Unani, Homeopathy, Chinese, as well as in the medicinal systems of aborigines. Medicinal plants are the sources of drug components, lead compounds, excipient, etc. of modern medicine. The secondary metabolites (e.g., alkaloids, phenolics, terpenoids, etc.) of drug plants provide the therapeutically active principles of herbal medicine, and more than 180 therapeutic principles of natural origin are used in modern medicine (e.g., ajmalicine, allicin, aspirin, artemisinin). In addition to wild sources, medicinal herbs are now cultivated by agronomic and biotechnological methods to meet the requirement of their smoothness and quality to consumers and trade market. The international market is expanding, about 2500 species of medicinal plants having about 400000 tons, and US$ 1.2 billion were traded during the 1990s and the value is likely to touch US$ 5 trillion by 2050.

Keywords Pharmacognosy · Crude drugs · Secondary metabolites · Herbal trade

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Pharmacognosy is involved in the studies of plants, animals, and other natural sources that yield crude drugs and drug substances including their taxonomic identity; chemical, physical, and biological properties of crude drugs; and methods of cultivation, harvesting, processing, storing, and marketing as well as extraction, preparation, and therapeutic use of crude drugs.

1.1 Therapeutic Use of Medicinal Plants and Their Extracts: A Historical Perspective

The medicinal use of plants and their extracts in health care is as old as the history of human society. Since ancient times, the natural products (e.g., products from plants, animals, minerals) have been the basis of treatment of human diseases in many cultures across the world. The beginning of the medicinal use of plants or their extracts was instinctive, people tried to use plants of their living environment for curing illness or discomfort, and they acquired knowledge about the therapeutic use of plants through tireless indiscriminate random efforts years after years but the exact time is yet to be explored. The archeological evidence related to the medicinal use of plants dates back to the Paleolithic period (at least 60,000 years ago), while the written evidence dates back to the Sumerians (over 5000 years ago). Papyrus, baked clay tablets, parchments, manuscript herbals, etc. are some examples of ancient recorded documents on the medicinal use of plants.

Different ancient cultures developed their own herbal system independently, almost in isolation but also some systems were developed elaborately in a more organized way (e.g., Chinese herbal medicine, Ayurveda, Unani) in the past. It is only at the beginning of the nineteenth century the term 'pharmacognosy' was coined for the first time by J.A. Schmid (1759–1809) in his handwritten manuscript 'Lehrbuch der Materia Medica', published in 1811 after his death, and later C.A. Seydler in 1815 use the term in his book 'Analectica Pharmacognostica' to mean the scientific study of medicinal herbs. Modern medicine recognizes herbalism as a form of alternative medicine. Phytotherapists use extracts from plants or parts of plants (e.g., whole herbs, roots or leaves seeds) but do not isolate particular phytochemicals. However, they now try to explain herb's actions in terms of their chemical constituents (Vickers and Zollman 1999; Langmead and Rampton 2001).

Medicinal plants are capable of synthesizing thousands of diverse bioactive constituents including alkaloids, terpenoids, phenolics, which are more efficient compared to a modern biosynthetic laboratory. The search for isolation of the active drug principles from plant extract began in the early part of the nineteenth century, and the first purely synthetic drugs based on natural products were formulated in the middle of the nineteenth century (Schulz et al. 2001). A large number of plant-derived active compounds is now used in modern medicine, and these compounds show a positive correlation between their modern therapeutic use and traditional use of the source plants (Fabricant and Farnsworth 2001; Pan et al. 2013).

Chemical compounds of herbal origin and that of the conventional drugs mediate their effects on the human body through similar processes, i.e., herbal medicines do not differ greatly from conventional drugs in terms of their mechanism of action and this enables herbal medicines to be as effective as conventional medicines (Lai and Roy 2004; Tapsell et al. 2006). Phytochemicals of medicinal plants and their extracts may function as analgesics, antitussives, antihypertensives, cardiotonics, antineoplastics, antimalarials, antioxidant, antiseptic, diuretic, nervous system stimulant, sedative, expectorant, digestive agent, etc. and play important role in the development of many clinically useful agents. Medicinal plant constituents like aspirin, atropine, opium, digitalis, dioxin, codeine, morphine, quinine, etc. have a long history of use in traditional as well as modern medicine. Drug principles like inulin, digoxin, morphine and codeine, quinine are derived from dahlias, foxglove, poppy, cinchona respectively (Meskin et al. 2002). Seven drug principles are now in use clinically for various types of cancers, e.g., taxol, vinblastine and vincristine, topotecan and irinotecan, and etoposide and teniposide derived from *Taxus* sp., *Catharanthus roseus*, *Camptotheca accuminata*, and *Podophyllum peltatum*, respectively (Patwardhan et al. 2003).

A large section of the population in developing countries, up to the present time, rely on traditional herbal medicine for their primary care need because it is affordable and easily accessible source of treatment (WHO 2001a, b, 2002a, b, c, 2005), although the development and mass production of chemically synthesized drugs over the past 100 years have revolutionized health care in most parts of the world. In Africa about 90% and in India 70% of the population depend on traditional medicine. In China, traditional medicine accounts for around 40% of all health care delivered, and more than 90% of general hospitals have units for traditional medicine (WHO 2005). Traditional medicine in the name of CAM is becoming more and more popular in the developed countries like Germany, Australia, Canada, USA, Belgium, France, etc. (Marstedt and Mochus 2002; WHO 2002a). Traditional systems' medicines have been serving the rural communities from antiquity; however, they were officially recognized in 1978 by the Alma-Ata Declaration on primary health care (PHC) as important resources in achieving health for all (WHO 1978). Safety, efficacy, and quality control of herbal medicines are still crucial and problematic because of many factors (e.g., lack of uniform standards and methods, inadequate research). Double-blind clinical trials may be helpful to ensure safety, efficacy, and quality of the herbal products (Vickers 2007).

Pharmacognosy has a long history of development, started with the desperate search for medicinal plants to alleviate illness in antiquity through guess work, trial and error, quackery, etc. and culminated into its development as a multidisciplinary science of crude drugs. It is now a branch of modern medicine that studies medicines from plant, animal, mineral, and other natural sources. Pharmacognosy includes phytochemistry as an important branch, concerned with the determination of the bioactive ingredients of medicinal plants, their origin, classification, quality and quantity assessment, methodology as well as analysis of their beneficial and harmful effects on human health. Phytochemistry also studies metabolomics in relation to functional genomics and systems biology.

1.2 Pharmacognosy: A Multidisciplinary Science of Crude Drugs

Pharmacognosy is the scientific study of crude drugs (fresh or dried and unprocessed material) from natural sources like plants, animals, and minerals. Pharmacognosy gives a sound knowledge of the vegetable drugs under botany and animal drugs under zoology. Plant, the oldest source of drugs, provides a large stock of rich, complex, and highly diversified structures of phytochemicals which are unlikely to be synthesized even in a biosynthetic laboratory. Almost all parts of the plants are used or drug source. For example, leaves of *Digitalis purpurea*, *Eucalyptus globulus*, *Nicotiana tabacum*, *Atropa belladonna*; flowers of *Syzygium aromaticum*, *Crocus sativus*, *Papaver somniferum*, *Catharanthus roseus*, *Rosa damascena*; fruits of *Coriandrum sativum*, *Citrullus colocynthis*, *Foeniculum vulgare*, *Senna* spp., *Physostigma venenosum*; seeds of *Nux vomica*, *Ricinus communis*, *Physostigma venenosum*, *Strophanthus* spp.; stem of *Chondrodendron tomentosum*, bark of *Cinchona* spp., *Holarrhena antidysenterica*, *Cinnamomum zeylanicum*, *Atropa belladonna*, *Hyoscyamus niger*; wood of *Quassia amara*, *Santalum album*; roots of *Carapichea ipecacuanha*, *Rauvolfia serpentine*; rhizome of *Curcuma longa*, *Zingiber officinale*, *Valeriana officinalis*, *Podophyllum peltatum*, etc. are some of the common crude drugs of plant origin. Similarly, animal source includes pancreas for insulin, urine of pregnant women for human chorionic gonadotropin (hCG), sheep thyroid for thyroxin, cod liver for vitamins A and D, anterior pituitary for pituitary gonadotropins, blood of animals for vaccines, stomach tissue for pepsin and trypsin, etc.; and minerals such as iron, mercurial salts, zinc as zinc supplement, gold salts, iodine, and iodine supplements are used for anemia, syphilis, wounds and in eczema, rheumatoid arthritis, antiseptic, and iodine supplements, respectively. Some of these, however, are now replaced by better drugs. Other animal sources include honey from bees, beeswax from bees, bufalin from toad, musk oil from musk, spermaceti wax from sperm whale, wool fat (lanolin) from sheep, carminic acid from cochineal, venom from snake, etc. Botanical source of crude drugs dominates over animal and mineral sources (Rates 2001). The term herb includes whole plant (e.g., *Eclipta alba, Euphorbia hirta, Centella asiatica*, etc.) and also different plant parts. Plant preparations, animal, and mineral products are said to be herbal or medicinal when they are used to promote health beyond basic nutrition.

The pharmacognostical study of crude drugs from plant and animal sources includes botany, zoology, chemistry, and pharmacology as basic subjects. Pharmacognosy embraces a broad spectrum of biological and socio-scientific subjects. Ethnobotany, marine biology, microbiology, biotechnology, phytochemistry, zoopharmacognosy, marine pharmacognosy, analytical pharmacognosy, herbal formulations, nutraceuticals, cosmeceuticals, etc. are also included as subject matter of pharmacognosy.

Botany and zoology include the identification (taxonomy), genetics, breeding, pathology, etc. Taxonomic identity is fundamental for pharmacopoeial and quality

control purposes, and by applying broader biological knowledge, one can improve the cultivation and culture methods for both plants and animals of therapeutic importance. Chemical characterization includes isolation, identification, and quantification of constituents in plant and other animated materials. Pharmacology studies the biological effects that the chemicals in medicinal plants and other natural sources have on cell cultures, animals, and humans (including pharmaceutics, clinical pharmacy). However, in the nineteenth century and even at the beginning of the twentieth century, pharmacognosy was a branch of medical science involving crude drug practices and the main focus was on the botanical aspects of the crude drugs such as description and identification of drugs in their whole state and in powder form for pharmacopoeial identification and quality control purposes.

Ethnobotany plays important role in drug discovery and many important modern drugs like digitoxin, reserpine, tubocurarine, ephedrine, ergometrine, atropine, vinblastine, and aspirin have been discovered by following leads from the folk uses (Anyinam 1995). Chemistry, pharmacology, microbiology, and biochemistry play vital role in pharmacognostical studies involved in isolation, identification, characterization, biotransformation, and discovery of lead compounds and new drugs from natural sources. Molecular biology, genomic science, biotechnology, and bioinformatic tools have a deep impact on drug discovery and development. Marine-derived bioactive pharmaceuticals and nutraceuticals provide a plethora of health benefits including antioxidant, anticancer, antiviral, anticoagulant, antidiabetic, antiallergy, anti-inflammatory, antihypertensive, antibacterial, and radioprotective activities (Barrow and Shahidi 2008; Venugopal 2008; Wijesekara et al. 2011). Zoopharmacognosy is a branch of pharmacognosy that deals with the self-medication behavior of non-human animals, and such behavioral study of animals may definitely enhance the discovery and development of new drugs. Analytical pharmacognosy, by applying different analytical methods, determines different physical and chemical constants such as ash values, extractive values, moisture content and loss on drying (LOD), volatile oil content, bitterness value, microbial load, pesticides, heavy metals and radioactive contaminants, foreign matters in various herbal drugs. Determination of Rf value following chromatography and chemical tests is important for quality control of herbal drugs. Adulteration of crude drugs is detected by microscopic, physical, organoleptic, chemical, biological, and other methods of evaluation. Herbal formulation indicates composition product (single or multiple herbs), dosage form (quantity), and provides other information regarding use (therapeutic, nutritional, cosmetic), benefits, and contradictions. Assessment of quality, stability, safety, and efficacy are essential for standard herbal formulation.

With the renaissance of pharmacognosy in the twenty-first century, the conventional botanical approach of pharmacognosy has been extended up to molecular and metabolomic levels (Huang et al. 2009; Dhami 2013). Pharmacognosy has been advanced and extended up to a significant extent to cover a wide spectrum of the natural medicine. Under the circumstances of prevalent adulteration, inappropriate formulation, intoxication, plant and drug interactions, etc. leading to life risk adverse or lethal reactions (Elvin-Lewis 2001; Talalay 2001), proper double blind

clinical trials are needed for the improvement of quality (identity, purity, consistency, etc.), efficacy (therapeutic indications, clinical studies, pharmacological investigations), safety (adverse reactions, drug interactions, contraindications, precautions) of the herbal products before recommendation for therapeutic use (Ernst 2007; Vickers 2007; Shinde et al. 2008; Blondeau et al. 2010).

1.3 Importance of Pharmacognosical Study and Development CAMs Concept

Pharmacognosical studies put due emphasis on origin and use of natural products as drugs, sweeteners, flavorings, colorings, cosmeceuticals, nutriceuticals, etc. Drugs of natural origin are intended for use in the diagnosis, cure, prevention, etc. of diseases, and they are staging a comeback all over the world. Many modern drugs available in the market for use today are obtained either directly from natural sources like plants, microbes, animals, and minerals or indirectly from synthetic and semisynthetic mechanism using the lead compounds of natural origin as a template (Fabricant and Farnsworth 2001). The extracts of folk medicine, natural products, or related substances account for 30% of the top 35 natural product-based drugs sold worldwide in recent years (Butler 2004). Natural products and their derivatives represent more than 50% of all the drugs in modern therapeutics (Pan et al. 2013). Over three-quarters of the world population and about 80% of the worlds' rural people rely on herbal medicine for primary health care (Sarkar 1996; WHO 2002c; Sakarkar and Deshmukh 2011). In developed country like USA, plant drugs constitute as much as 25% of the total drugs, while in developing countries like China and India, the contribution is as much as 80% (Joy et al. 1998). Herbal medicines have all-natural ingredients, readily available, much cheaper compared to high-value Western medicine; they provide an excellent source of alternative medicinal therapy, very effective with chronic conditions (arthritis), do not result in long-term effects on the body, have multipurpose benefits (ginger, peppermint), good in boosting the immune system, best for people who are allergic to various types of drugs, and can be used to cure people of all ages. It is also believed that herbal drugs are safer and more effective with fewer side effects than modern pharmaceutical drugs. High value of the modern Western drugs discourses many people living in the developing countries as they need to spend about 40–50% of their total wealth for health care purposes Thus, the use and popularity of medicinal plants from which the herbal drugs are produced is much more in the developing countries than the developed world. However, herbal medicines have some negative aspects, e.g., non-availability of prescription or dosage for herbal medicines, they are slow in action, not good for serious trauma (broken bones) or heart attack, can react with the pharmaceutical drugs, unregulated, some are not safe to use, some are toxic and need professional supervision (calamus, comfrey, chaparral, etc.).

Table 1.1 Usage of TCAM in developing and developed countries in % of the population

Developing Country	Usage of CAM in %	Developed Country	Usage of CAM in %
Uganda	60	Belgium	31
Tanzania	60	USA	42
Rwanda	70	Australia	48
India	70	France	49
Benin	80	Canada	70
Ethiopia	90	–	–

Source WHO (2002a). Traditional Medicine Strategy 2002–2005, World Health Organization, Geneva

The herbal drugs, sweeteners, flavorings, colorings, cosmeceuticals, nutriceuticals, etc. today symbolize safety in contrast to the synthetics that are regarded as unsafe to human and environment. The dependence on synthetics of the modern age is over and people are returning to the naturals with hope of safety and security. The increase of population, inadequate supply, high price of allopathic drugs, high cost of treatment, side effects, and development of microbial resistance to antibiotic drugs have led to the increased dependence on the use of herbal medicines for a wide variety of diseases (Pathare and Wagh 2012). Plants have been used successfully as medicines in every continent throughout the history. The practice of herbal medicine is well established in Asia and Africa, and the use of herbal products as complementary and alternative medicines (CAMs) is becoming popular rapidly in Europe, North America, and Australia (Table 1.1). Now, the use of phytomedicines as well as phytonutrients (nutraceuticals) continues to expand rapidly across the world for the treatment of various diseases (WHO 2004).

1.4 Medicinal Plants and Their Metabolites of Pharmacognostical Importance

Out of the total 250,000–500,000 plant species on earth (Borris 1996), more than 80,000 are known as medicinal plants and about 35,000–70,000 species are used medicinally across the world. The number of medicinal plants used in different countries may exceed 1000 species (Sofowora 1993). A list of medicinal plants prepared by WHO from the late 1970s contained 21,000 species (Penso 1980), and now it is assumed that, out of the global total 422,000 flowering plant species, the number of plant species used for medicinal purposes across the world is more than 50,000 (Govaerts 2001; Bramwell 2002; Schippmann et al. 2002). However, only 1–10% of them have been studied chemically and pharmacologically for their potential medicinal value (Verpoorte 2000).

In China, 4941 species plants out of the total 26,092 are used (18.9%) as drugs in traditional medicine (Duke and Ayensu 1985). In India, more than 45000 different plant species grow, and out of them, about 15,000–20,000 plants (3.3–4.4%) have

good medicinal value. However, only 7000–7500 species are used by traditional communities for medicinal purposes (Joy et al. 2001). In Bangladesh, more than 5000 higher plant species grow (Mia 1990) and about 1000 plant species (20%) are considered to have medicinal properties. About 455–747 plant species of Bangladesh have been described with their specific medicinal properties (Ghani 2003; Yusuf et al. 2009). Most of these medicinal plants are used in the preparation of Ayurvedic, Homeopathic, Unani, and other indigenous systems of medicine in Bangladesh. Among the indigenous systems of medicine, Ayurveda and Unani are most ancient (1500–800 BC), most developed, and widely practiced in the Indian subcontinent. Traditional medicines are also practiced in Tibet, Mongolia, and Thailand. China has demonstrated the best use of herbal medicine in providing primary health care, and its use dates back to 3000 BC, when the Chinese were already using over 350 herbal remedies.

The herbal drugs are derived from whole plant and different organs of plant (organized drugs), and also some drugs are prepared from excretory plant products (unorganized drugs). Green plants synthesize alkaloids, phenolics, terpenoids, and a variety of other secondary metabolites. The terms 'secondary metabolites' and 'natural products' are synonymous, exhibit very wide structural diversity (Kinghorn et al. 2009), and can be found as active ingredients in non-prescription and prescription drugs (pharmaceuticals) as well as in other herbal products (Gurib-Fakim 2006; Schmidt et al. 2007). Among the innumerable number of bioactive therapeutic principles of plant origin used in modern medicine, some of the examples are ajmalicine, allicin, aspirin, artemisinin, atropine, berberine, camptothecine, capscicine, catechin, cocaine, codeine, curcumin, digoxin, diospyrin, digitoxigenin, digoxigenin, elipticine, emetin, ephedrine, forskolin, glycyrrhizin, gossypol, homoharringtonine, indicine N-oxide, magnolol, morphine, nerrifolin, nimbidin, paclitaxel, pilocarpine, plumbagin, podophyllin, podophyllotoxin, pristimerin, quassinoids, quinine, rescinnamine, reserpine, ricin, scopolamine, sophoradin, taxol, thevenerin, topotecan, tubocurarine, vinblastine, and vincristine. These alkaloid, phenolic, and terpenoid compounds constitute the pharmacologically active drug principles, and these bioactive secondary metabolites are synthesized by two principal pathways: (i) shikimic acid pathway that produces a pool of aromatic amino acids leading to the synthesis of phenolics (lignins, tannins, quinines) and alkaloids and (ii) acetyl-CoA mevalonic acid pathway in which a vast array of terpenoids are formed (Eisenreich et al. 2004; Mustafa and Verpoorte 2007; Ramawat et al. 2009). They are the examples of single entity plant drugs, which mostly treat serious medical disorders and at present about 50% of the total plant-derived drug sales come from single entities, while the remaining 50% come from bulk herbal remedies. Where the active molecule cannot be synthesized economically, the product must be obtained from the cultivation of medicinal plant. Allicin, aspirin, artemisinin, atropine, camptothecin, capscicine, codeine, curcumin, digitoxigenin, digoxigenin, ephedrine, gitoxigenin, morphine, podophyllotoxin, taxol, and tubocurarine are among those major plant drugs for which no synthetic one is currently available. Some important chemical intermediates useful for manufacturing the modern drugs are also obtained from plants (e.g., diosgenin,

solasodine, β-ionone). Modern medicine has adopted a number of plant-derived drugs, viz. (a) anticancer drugs (ajmalicine, vinblastine, vincristine from *Catharanthus roseus*), (b) hypotensive-tranquilizer drugs (rescinnamine, reserpine from *Rauvolfia serpentina*), (c) antimalarial drug (quinine from *Cinchona sp.*), and (d) antiglaucoma drugs (pilocarpine from *Pilocarpus jaborandi*). The estimated value of plant-based drugs is nearly US$ 45000 million a year.

1.5 Pharmacognosy and Trade of Medicinal Plants

Plant-derived drugs offer a stable market worldwide, and plants continue to be an important source for new drugs. The international trade in herbal products is a large and expanding trade. It is estimated that about 2500 species of medicinal plants are traded in the international market (Hersch-Martínez 1995). An average of 400,000 tons of medicinal plants, valued at US$ 1.2 billion, was estimated to be traded annually during the 1990s (Heywood 2000). The world market for plant-derived drugs and aromatics may account for >US$ 70 billion and is likely to touch US$ 5 trillion by 2050. The main markets include Europe, North America, and Asia. Europe, which accounts for about 50% of the world market, is the largest (Anonymous 2000). The three leading exporting countries are China, India, and Germany (Kate and Laird 1999). India, a close neighbor of Bangladesh, ranks second in the world after China in the export of medicinal plants. The global trade of medicinal plants stands at US$ 7592 million in 2011, and of these China and India's share were around US$ 1329 million and US$ 790 million, respectively. On the other hand, Bangladesh earns about US$ 20,000–25,000 annually by exporting roots of *Rauvolfia serpentina* and expends a huge amount of foreign exchange for importing many useful herbs. The scientific study of traditional medicines, derivation of drugs through bio-prospecting and systematic conservation of the concerned medicinal plants are thus of great importance.

Forests are veritable storehouses of biological diversity (at genes, species and ecosystems levels) and forest biodiversity is the basis for more than 5000 commercial products including herbal medicine, food and clothing (Anonymous 2011). Deforestation, forest degradation, depletion, indiscriminate extraction of forest resources etc. are major threats to biodiversity and generation of commercial products worldwide. With forest biotopes being an irreplaceable source of new drugs (e.g., taxol), deforestation can destroy genetic variations irretrievably. The major system of indigenous herbal medicine (e.g., Ayurveda, Unani) in Bangladesh, as elsewhere in the world, has reached a very critical phase due to scarcity of raw drugs because of deforestation, degradation, and others. Natural forests, the living treasure of plant and animal diversity, have already been destroyed, left about 8% only at present as against a mandatory 25% of the land area of Bangladesh. Many valuable medicinal plants are under the verge of extinction. The 'Red Data Book of Vascular Plants of Bangladesh' has 427 entries of endangered species, of which 28, 124, 81, 100, and 34 are considered extinct,

endangered, vulnerable, rare, and insufficiently known species, respectively (Khan et al. 2001). Natural forest should be regenerated, and forest biodiversity should be conserved for the sake of the indigenous systems of herbal medicine and others because forest provides habitat for innumerable plants, animals and microorganisms; maintains delicate ecological balance, conserves soil and water, and controls floods, drought, and pollution.

1.6 Traditional and Modern Pharmacognosy

Herbal medicine as the oldest science has been in use to alleviate disease and suffering of human being ever since the onset of primitive civilization. The use of plant, animal, and mineral products in the treatment of disease as well as their trade between cultures have been known for thousands of years. About 200 years have been elapsed since the term 'pharmacognosy' was introduced by J.A. Schmidt (1759–1809) for the first time and C.A. Seydler used this term in his book in 1815. Traditional pharmacognosy at the beginning was concerned mainly with flowering plants and their products and later on other groups of organisms including animals, marine organisms, and microbes were considered as legitimate material for study by pharmacognosists. Pharmacognosy has evolved considerably during the past 200 years. At the beginning of the twentieth century, pharmacognosy was developed mainly on the botanical side and was concerned with the description and identification of the crude drugs as well as with their history, collection, preparation, storage, and trade. Before the advent of modern analytical chemistry, emphasis was on the traditional botanical techniques such as macroscopical and microscopical characterizations of plant material for identification of crude drugs, differentiation of crude drugs from related species, and detection of adulteration. Microscopy was the only method of much use when the drug was in powdered or finely broken form. Traditional pharmacognosy emphases identification, authentication, and quality control of crude drugs. Identification of crude drugs required the basic knowledge of the subject botany and which are evident from the earliest records of medical history depicted in many ancient stones, bones, papyri, and texts of herbal medicine. For centuries, botany was a part and parcel of medicine because plant identification was a prerequisite for all physicians in the development of drugs. In fact, there have been notable developments in different areas of traditional pharmacognosy including production, isolation, and characterization techniques of drug principles, conservation of source materials, and commerce of the crude drugs. Some plants when their local wild sources become exhausted due to over extraction (e.g., *Catharathus roseus*, *Coleus forskohlii*, *Arnica montena*, *Taxus brevifolia*, *Leucojum aestivum*) necessitate conservation, cultivation, and/or artificial production by cell or tissue culture in order to avert the supply crisis. In recent times, more significant is the acceptance and inclusion of crude drugs as potential plant products in different national and international pharmacopeia like the European pharmacopoeia, the British pharmacopoeia, Chinese pharmacopoeia, Japanese

pharmacopoeia, Indian pharmacopoeia, etc. as well as in the pharmacopoeia compiled by the WHO in response to the continued public demand for herbal medicine. The guidelines outlined in such pharmacopoeia are mainly to ensure smooth supply and quality control of herbal products (WHO 1998, 2007). Traditional pharmacognosy is still of fundamental importance but developments in other scientific fields have enormously expanded and elevated the subject to the level of modern pharmacognosy.

In the recent years, pharmacognosy has made a revolutionary come back with a more significant role in primary health care of the rural people, and according to WHO, ~70% of the world population depend on herbal medicine for primary health care purposes and some 35,000–70,000 species of plants equivalent to 14–28% of the world 250,000 plants species have been used as medicaments (Farnsworth and Soejarto 1991; Akerele 1992; Padulosi et al. 2002). Medicinal plants are continuously contributing to the development of modern drugs, and >50 major drugs available in the global market are originated from tropical plants (De Padula et al. 1999) and 89 plant-derived drugs currently prescribed in the industrial world were discovered by studying traditional herbal use (Fransworth 1992; Balick and Cox 1997).

The nineteenth century was a significant period for pharmacognosy when several hundred texts on materia medica and medical botany were published describing thousands of medicines used then across the world and provided information regarding plant origin, harvest, chemistry, processing, and morphological characteristics. Pharmacognosy in the second half of the twentieth century has evolved considerably following advances in disciplines such as taxonomy, agronomy, enzymology, genetics, analytical chemistry, natural drug evaluation techniques, quality control, pharmacology. Modern pharmacognosy deals with phytochemical and pharmacological aspects of natural products along with their classical matters. Advances in chromatography, spectroscopy, thin-layer chromatography, etc. enabled the pharmacognosists for isolation and structural characterisation of phytochemicals. In recent years, pharmacognosy has regained importance due to the renewed interest in natural products as lead compounds for modern medicines and rise of popularity in use of natural products in the developed countries as complementary medicine. At present, pharmacognosy has expanded beyond traditional techniques and advances in molecular biology and high throughput screening (HTS) methods to identify chemical constituents in enormously large scale and therapeutic targets and bioassay-guided fractionation have transformed the field. Plants are the inexhaustible source of new drug compounds, and a large number of plant species are constantly being screened for their cytotoxic, antibiotic, antiamoebal, anti-inflamatory, anti-hypertensive, anti-hyperglycemic, anti-Parkinsonism, etc. activities. Currently, new methods of drug discovery utilizing computer simulation models have been developed to complement the traditional process of investigating potential new drugs based on ethnopharmacological observations. High throughput screening is a quick process of drug-discovery and is widely used in the pharmaceutical industry to quickly assay the biological or biochemical activity of a large number of drug-like compounds.

Modern pharmacognosy is a highly specialized science dealing with biological, biochemical, and medicinal properties of plants, natural raw material and its products. It is also a highly multidisciplinary collaborative science ensconced at the interface of so many subjects including biology, biochemistry, chemistry, sociology, computer science. The topics of study in pharmacognosy are medicinal plants, medicinal plant material, products of animal origin and minerals. Instead of the conventional Galancial preparation, the use of single pure compound, natural or synthetic, has become a general practice in herbal and homeopathic systems of treatment. Modern pharmacognosy as an interdisciplinary subject has entered a new era at molecular level, the molecular pharmacognosy, at the beginning of the twenty-first century.

1.7 New Trends in Pharmacognosy

Pharmacognosy was initiated as a descriptive botanical subject of crude drugs chiefly concerned with the description, identification, and authentication of crude medicinal materials of natural sources, their standards, relate their chemical build-up in relation to their geographical locations, their constituents and uses, etc. During the early nineteenth century, abotanico chemical approach was framed to Pharmacognosy. At the beginning of the twentieth century, pharmacognosy was still a descriptive botanical subject mainly concerned with the description and identification of the crude drugs as well as their history, collection, preparation, storage, and trade and continued up to the first half of the twentieth century, and before the advent of modern analytical chemistry pharmacognosy was taught and practiced as descriptive botanical subjects. In the second half of the twentieth century, pharmacognosy has evolved considerably following advances in disciplines such as taxonomy, agronomy, enzymology, genetics, phytochemistry, analytical chemistry, natural drug evaluation techniques, quality control, pharmacology. A new era of scientific development of pharmacognosy was initiated with the development and contribution of other branches of science. Different branches like clinical pharmacognosy, analytical pharmacognosy, industrial pharmacognosy, etc. have already been established, and these reflect the contemporary advancement and diversification of the subject (Dhami 2013).

With the advancement of other branches of science, e.g., biotechnology, molecular biology, phytopharmacology, etc., pharmacognosy as a subject has got newer directions and now has embraced many new areas of activities in the arena of natural medicine as indicated below:

(i) Pharmacognosy has evolved after the second half of the twentieth century from a descriptive botanical subject to a science embracing the chemistry and pharmacology of crude composites as well as pure active principles in the twenty-first century.

(ii) Development of phytochemistry and natural product chemistry led the discovery and development of valuable natural therapeutic agents including atropine, digitoxin, ephedrine, morphine, galanthamine, paclitaxel, artemisinin, etc. (Jones et al. 2006). Many other natural compounds such as curcumin, epigallocatechin-3-gallate (EGCG), resveratrol, and quercetin have attracted researchers' attention for treatment of cancer and cardiovascular diseases (Lin et al. 2012; Koeberle and Werz 2014; Zheng et al. 2014).

(iii) Using novel formulations, researchers have recently attempted to improve pharmacokinetics of the natural compounds, e.g., attachment of paclitaxel to gold nanoparticles via DNA linkers (Zheng et al. 2014), encapsulation of curcumin by beta-case in nanomicelle (Esmaili et al. 2011), etc. Various novel pharmaceutical systems such as nanoparticles, liposomes, micelles, and phospholipid complexes, drug-encapsulated polymer nanoparticles, nanogels, etc. have been used to improve bioavailability, stability, and efficacy of compounds such as curcumin, quersetin, sylimarin, and so on (Ajazuddin 2010; Coimbra et al. 2011).

(iv) Development of neuropharmacognosy as a discipline at the interface of both pharmacognosy and neurosciences and the complexity of neuropharmacognosy comes from the multidisciplinary characters of both pharmacognosy (includes pharmacology and phytochemistry) and neurosciences (covers neurobiology, neurophysiology and neuropharmacology). The existence of both pharmacological and toxicological aspects of neuropharmacognosy creates more challenges.

Plant neurobiology has emerged in recent years as a result of the incorporation of new research knowledge generated in the field of plant electrophysiology, cell biology, molecular biology, and ecology (Brenner et al. 2006). Plant neurobiology focuses on natural products whose biosynthesis is shared by animal and plant organisms, i.e., indoleamines (melatonin and serotonin) and catecholamines (dopamine, norepinephrine and epinephrine) (Iriti 2013).

(v) Advancements in isolation and purification techniques with the latest technology for bioassays and molecular techniques have encouraged the modern pharmaceutical science towards analytical aspects of Pharmacognosy. Pharmacognosy research started to emphasize on isolation and structure elucidation of biologically active principles from natural resources worldwide.

(vi) At present, cultivation, collection, authentication, identification, quality assessment, biochemical, biological, and molecular studies of natural drugs are being considered as the main aspects of Pharmacognosy. As a result, the modern curriculum of pharmaceutical sciences has undergone substantial changes, and pharmacognosy has become one of the core streams of pharmaceutical research and education.

(vii) Cell biotechnology is widely recommended now as a new possibility for the production of plant secondary metabolites of known pharmaceutical activities. Besides the enormous possibilities of biotechnological production of

pharmaceuticals using microbial, plant, insect, or mammalian cells, biotechnology offers also genetic engineering as an important new technology for the production of high-tech herbal products. Clinical pharmacognosy, analytical pharmacognosy, and industrial pharmacognosy have been established that represent the contemporary advancements in the field of pharmacognosy. Furthermore, molecular pharmacognosy, genomic pharmacognosy, metabolomic pharmacognosy, etc. have been deemed as the promising approaches to pharmacognosy research.

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Chapter 2
Origin, Definition, Scope and Area, Subject Matter, Importance, and History of Development of Pharmacognosy

Abstract The term 'pharmacognosy' was derived by the merger of two Greek words (e.g., pharmakon—drug and gnosis—knowledge of) to mean the knowledge of drugs. It was introduced and used for the first time by J.A. Schmidt (1811) and C.A. Seydler (1815), respectively, to define the branch of medicine or commodity which deals with crude drugs. Studies on physical, chemical, biochemical, and biological properties of drugs, drug substances, or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources are now included in pharmacognosy. Pharmacognosy was developed as a descriptive botanical subject in early days (nineteenth and during the last half of the twentieth century), and currently, plant-based drugs are researched and formulated in modern framework of medicine rather than galenical preparations. Pharmacognosy has been playing a significant role in the discovery, characterization, production, and standardization of natural drugs. Therefore, the scope of pharmacognosy is broad and includes the scientific study of crude drugs, medicinal products (e.g., enzymes, vitamins, antibiotics, pesticides, allergens, and allergenic extracts), and excipients (e.g., coloring, flavuring, emulsifying and suspending agents, diluents, bulking or filler agents, disintegrants, anesthetic aids, sweeteners, binders, adhesives, solidifiers and also the research problems in the areas of phytochemistry, microbial chemistry, biosynthesis, biotransformation, chemotaxonomy, and other biological and chemical sciences. Studies on poisonous, hallucinogenic, and teratogenic plants; raw materials for the production of oral contraceptives, aphrodisiacs, etc., as well as spices, beverages, and condiments are included in the subject matters of pharmacognosy. The history of development of pharmacognosy is as old as that of human history as evidenced by the Neanderthals use of healing herbs such as yarrow, marshmallow before >60,000 years. The innovation of medicinal properties of plants at the beginning was accomplished through guesswork, observation, trial and error, accidental discovery, curiosity, and search for food and in many other ways. The ancient people acquired a considerable volume of knowledge about drugs by a combination of all these means and subsequently a group of people (medicine men) emerged in the society who acquired expertise in collecting, testing, and using medicinal plants for treating diseases. The ancient Egyptian, Babylonian or Assyrian, Indian, Chinese, Greek, and Roman were the forerunner of herbal medicine and contributed

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enormously to the development of pharmacognosy. The knowledge developed on herbal medicine was once transferred to successors verbally by the use of signs and symbols, and the earliest written form was the Egyptian papyri. This was followed gradually by backed clay tablets, parchments, manuscript herbals, printed herbals, pharmacopoeias and recently by computerized information database systems.

Keywords Scope of pharmacognosy · Medicinal products · Excipients · History of pharmacognosy

2.1 Origin, Definition, Scope, and Avenue of Pharmacognosy

The term 'pharmacognosy' was coined for the first time by an Austrian physician J.A. Schmidt (1759–1809) in his hand-written manuscript 'Lehrbuch der Materia Medica,' published in 1811 after his death and C.A. Seydler used the term in his book on crude drugs 'Analectica Pharmacognostica' in 1815. Pharmacognosy has been derived by the merger of two Greek words: (a) 'pharmakon' means a drug, and (b) 'gnosis' means knowledge of or 'gignosco' means to acquire knowledge of. Pharmacognosy means knowledge of drugs or to acquire knowledge of drugs. During the nineteenth century and the beginning of the twentieth century pharmacognosy was used to define the branch of medicine or commodity which deals with drugs in their crude or unprepared form from natural sources. The American Society of Pharmacognosy describes 'pharmacognosy' as the study of physical, chemical, biochemical, and biological properties of drugs, drug substances, or potential drugs or drug substances of natural origin as well as the search for new drugs from natural sources (Photograph 2.1). Although most pharmacognostic studies focus on plants and medicines derived from plants, other types of organisms such as microbes (bacteria, fungi, etc.), marine organisms, and animals are also important in pharmacognosy. It is the science of nature-derived pharmaceuticals and includes studies on structural, physical, chemical, biological characters of crude drugs their therapeutic use, history, method of cultivation, collection, preparation, preservation, and commerce.

The scope of pharmacognosy is broad in the field of pharmacy. Pharmacognostical studies include natural product molecules, especially the secondary metabolites, which are useful for their medicinal, ecological, gustatory (that distinguishes sweet, sour, bitter, and salty taste properties in the mouth), or other functional properties. In early part of the nineteenth century, the term 'Pharmacognosy' was coined; during the last half of the twentieth century, pharmacognosy was evolved from being a descriptive botanical subject to one having a more chemical focus embracing a broad spectrum of disciplines including botany, zoology ethnobotany, marine biology, microbiology, herbal medicine, chemistry, biotechnology, phytochemistry, pharmacology, pharmaceutics, clinical pharmacy, pharmacy practice, etc.; today, it is a highly interdisciplinary science. At the

Photograph 2.1 Research materials in the pharmacognosy laboratory: drugs from natural sources

beginning of the twenty-first century, pharmacognosy teaching in academic pharmacy institutions has been given new relevance as a result of the explosive growth in the use of herbal medicines. Pharmacognosy is now undergoing major change, and herbal drugs are researched and formulated in the modern framework of medicine instead of galenical preparations or conventional dosage. Pharmacognosy now embraces a wide range of diverse techniques, and the recent progress in extraction, chromatography, hyphenated techniques, screening of natural product, biotechnology, etc., has opened new avenues and lines for pharmacognosist to enhance natural product research. Herbs can be turned into products now, and pharmacognosis is playing active role in the discovery, characterization, production, and standardization of natural drugs.

Pharmacognosy is an important branch of pharmacy that includes the scientific study of structural, physical, chemical, biochemical, and biological properties of crude drugs and search for new drugs from plant, animal, and mineral sources. In addition, pharmacognosy studies of a variety of commercial and medicinal products such as vitamins, enzymes, pesticides, allergens as well as the study of history, distribution, cultivation, collection, preparation, identification, evaluation, preservation. and commerce of medicinal plants. Research problems in pharmacognosy include studies in the areas of phytochemistry, microbial chemistry, biosynthesis, biotransformation, chemotaxonomy, and other biological and chemical sciences.

2.2 Subject Matter of Pharmacognosy and Classification

Pharmacognosy is a branch of pharmaceutical science, and it is involved in the scientific study of crude drugs and active principles including their structural, physical, chemical and biochemical, therapeutic, and economic features.

(i) Natural source and its drug principles are important subject matter of pharmacognosy. For example, creat (*Andrographis paniculata*) and its labdane diterpenoid and rographolide; purple foxglove (*Digitalis purpurea*) and its cardiac glycoside digitoxin, digoxin; periwinkle (*Catharanthus roseus*) and its anticancer agents, vinblastine and vincristine; St. John's Wort (*Stramonium*) and its chemical constituents tropane alkaloids, hyoscine and hyoscyamine; Indian snakeroot (*Rauvolfia* root) and its alkaloids, ajmalicine, reserpine, and rescinnamine; fruits such as papaya (*Carica papaya*), kiwifruit (*Actinidia deliciosa* and other species), pineapple (*Ananas comosus*), figs (*Ficus carica*) and their proteases enzyme mixture; thyroid gland and its extracted hormone, thyroxin; pancreas and its peptide hormone, insulin, etc. are equally important as subject matters of pharmacognosy.

(ii) Excipients (pharmaceutic necessities) such as the coloring (*Curma longa, Crocus sativus, Carthamus tinctorius, Calendula officinalis*) and flavoring agents (*Mentha arvensis, Cymbopogon flexuosus, C. martini, Cyperus scariosus, Eucalyptus globules*); emulsifying and suspending agents (*Plantago ovata*); diluents, bulking agents or filler (plant cellulose as well as lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and magnesium stearate), and disintegrants (carboxymethyl cellulose); anesthetic aids (*Cannabis sativus, Piper methysticum*); sweeteners (*Glycyrrhiza glabra, Stevia rebaudiana*); binders (non-starch polysaccharides—pectins, alginates—and proteins-gelatin); adhesives (guar gum, amylase, and karaya gum); solidifiers (beeswax, cocoa butter, or theobroma oil), etc., are studied as important subject matters of pharmacognosy. Natural excipients are used in the formulation and preparation of pharmaceutical products because they are highly stable, modifiable, compatible, biodegradable, inexpensive, easily available, safe, and non-toxic in contrast to their many synthetic counterparts (e.g., maltodextrin, povidone or polyvinylpyrrolidone (PVP), polyethylene glycol-3350), and thus, they have a major role to play in pharmaceutical industry. In addition, natural excipients (e.g., pectin, agar, gelatin, wax, fixed oils) function as carrier or vehicles to ensure safe and targeted delivery of the active drug constituents of tablets and capsules.

(iii) The surgical dressings prepared from natural fibers, filtering agents such as diatomite, support media, and many areas of natural paramedics are now included in the subject.

(iv) Beverages such as tea and coffee are also studied in pharmacognosy because of their caffeine content that has good medical applications as an analgesic and stimulant.

(v) Pharmacognosy includes studies on poisonous (e.g., *Abrus precatorius, Atropa belladonna, Colchicum autumnale*), hallucinogenic or psychoactive (e.g., *Cannabis sativa*, *Datura stramonium*, *Ipomoea purpurea, Salvia divinorum*), and teratogenic (e.g., *Datura stramonium*, *Lupinus formosus, Nicotiana glauca*, *Conium maculatum*) plants.

(vi) Raw materials for the production of oral contraceptives (*Dioscorea alata, D. villosa*), aphrodisiacs (*Epimedium*, *Glycyrrhiza glabra, Smilax ornate*, *Turnaria aphrodisiaca*, ginger, ginseng, *Ginkgo biloba*), allergens, enzymes, vitamins, antibiotics, herbicides, and insecticides.

(vii) Studies of some spices and condiments are included in the subject matters of pharmacognosy as they possess definite medicinal and pharmaceutical properties. Bark of cinnamon (*Cinnamum zeylnicum*); cardamom (*Amomum aromaticum* and *A. subulatum*); fruit and various fruits of Apiaceae such as fennel (*Foeniculum vulgare*); coriander (*Coriandrum sativum*); cumin (*Cuminum cyminum*), anise (*Pimpinella anisum*); seeds of mustard (*Brassica alba, B. juncea, B. nigra*); flower bud of clove (*Syzygium aromaticum*); and rhizome of ginger (*Zingiber officinale*) are some typical examples of such articles.

(viii) The subject also includes many other aspects of plant science such as history, distribution, methods of cultivation, collection, identification, structure, drug preparation, evaluation, preservation, use and commerce of medicinal plant and plant products as well as use of biotechnological method for the production of active drug principles.

(ix) The pharmacognostical studies of crude drugs from plant and animal sources include botany, zoology, chemistry, and pharmacology as basic subjects. Botany and zoology include the identification (taxonomy), genetics, breeding, pathology, etc. Taxonomic identity is fundamental for pharmacopoeial and quality control purposes, and by applying broader biological knowledge, one can improve the cultivation and culture methods for both plants and animals of therapeutic importance. In the nineteenth and even at the beginning of the twentieth century, botany played role in pharmacognosy for botanical description and identity of the crude drugs in their whole state and in powder form for pharmacopoeial identification and quality control purposes. Chemical characterization includes isolation, identification, and quantification of constituents in plant and other animate materials. Pharmacology studies the biological effects that the chemicals in medicinal plants and other natural sources have on cell cultures, animals, and humans (including pharmaceutics, clinical pharmacy). Chemistry, pharmacology, microbiology, and biochemistry play important role in pharmacognostical studies involved in isolation, identification, characterization, biotransformation, and discovery of lead compounds and new drugs from natural sources.

(x) Pharmacognosy also includes ethnobotany (traditional use of plants for medicinal purposes plays important role in drug discovery); ethnopharmacology (pharmacological aspects of traditional medicinal substances);

phytotherapy (the medicinal use of plant extracts); phytochemistry (diversity of phytochemicals, identification of new drug candidates); zoopharmacognosy (animals self-medication by using plants, soils, and insects); biotechnology (synthesis of natural bioactive molecules using biotechnology); herbal interactions (interactions of herbs with other drugs and body); and marine pharmacognosy (use of and chemicals derived from marine organisms), analytical pharmacognosy, herbal formulations, nutraceuticals, cosmeceuticals, etc. Herbal formulation indicates composition product (single or multiple herbs) and dosage form (quantity) and provides other information regarding use (therapeutic, nutritional, cosmetic), benefits, and contradictions.

(xi) Molecular biology, genomic science, biotechnology, and bio-informatic tools have a deep impact on drug discovery and development. Analytical pharmacognosy, by applying different analytical methods, determines different physical and chemical constants such as ash values, extractive values, moisture content and loss on drying (LOD), volatile oil content, bitterness value, microbial load, pesticides, heavy metals and radioactive contaminants, foreign matters in various herbal drugs. Determination of Rf value following chromatography and chemical tests is important for quality control of herbal drugs.

(xii) Adulteration of crude drugs is detected by microscopic, physical, organoleptic, chemical, biological, and other methods of evaluation. Assessment of quality, stability, safety, and efficacy is essential for standard herbal formulation. Proper double-blind clinical trials are needed for the improvement of quality (identity, purity, consistency, etc.), efficacy (therapeutic indications, clinical studies, pharmacological investigations), safety (adverse reactions, drug interactions, contraindications, precautions) of the herbal products before recommendation for therapeutic use (Ernst 2007; Vickers 2007; Shinde et al. 2008; Blondeau et al. 2010). With the renaissance of pharmacognosy in the twenty-first century, the conventional botanical approach of pharmacognosy has been extended up to molecular informatic and metabolomic levels (Huang et al. 2009; Dhami 2013). Pharmacognosy considers all these as its subject matter.

2.3 Contribution of Pharmacognosy in Pharmacy and Pharmacology

(i) Pharmacognosy, the science of crude drugs of natural origin, occupies an important place in pharmacy. Pharmacognosy provides information about a large group of drugs and excipients from natural sources useful for screening, discovery, and development of modern pharmaceutical drugs.

(ii) Pharmacognosy supplies the general information about solubility, reactivity, stability, toxicity, dosage, availability, purity and yield, methods of isolation, purification, and identification of the chemicals of natural drugs to all practicing pharmacists. A thorough understanding of the active principles of natural drugs as chemicals is necessary for a successful practice of the pharmacists. Thus, pharmacognosy has become a discipline of increased significance in the curriculum of pharmaceutical education.

(iii) Pharmacognostical information on identity, physical nature, and chemical constituents of the drug principles is essential for understanding their pharmacological activities.

Chemical nature and properties of a drug principle can be studied and understood, or it can be synthesized or its activity can be modified or improved by a pharmaceutical chemist having a good knowledge in pharmacognosy about of its source, occurrence, method of isolation, and state of purity.

(iv) Formulation and preparation of a pharmaceutical product, pharmaceutics, are dependent on a number of properties, such as solubility, stability, reactivity of the ingredients. A pharmacist can earn this type of information on substances of natural origin from pharmacognosy.

(v) Price of a pharmaceutical product from natural sources or containing substances of natural origin is influenced by different pharmacognostical criteria such as the number of constituents from plant or animal constituents, methods of collection, curing, drying, and assaying of the ingredients. Thus, pharmacognosy is intimately associated with the curriculum of pharmacy administration dealing with prescription and pricing.

The relationship of pharmacognosy with operative pharmacy and dispensing is very intimate.

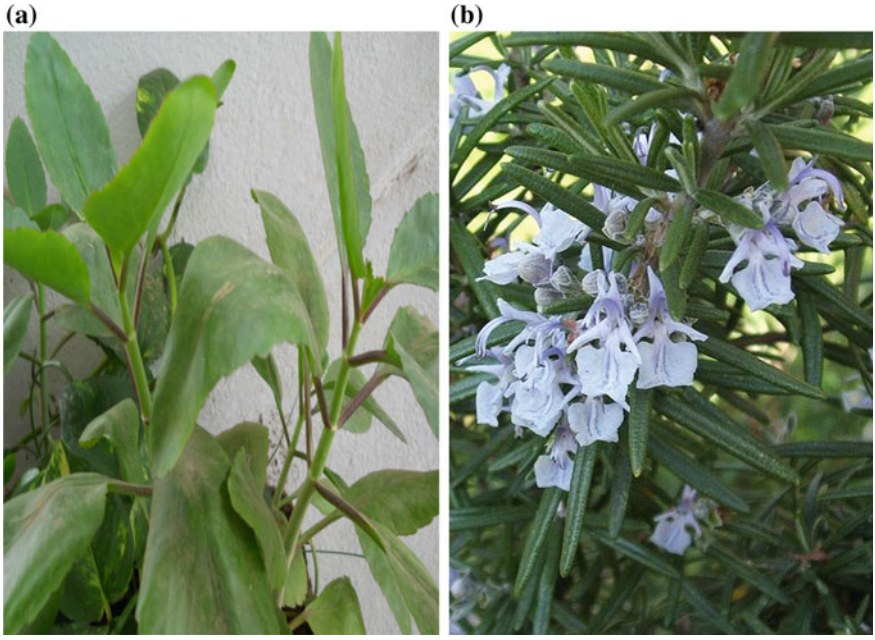
(vi) Pharmacology, an important branch of pharmacy, deals with the research, discovery, development, and characterization of drugs, and therefore, it is intimately associated with the life cycle of any drug (e.g., discovery and research, development, regulatory review and approval, commercialization). Pharmacognostical studies provide most of the information about authenticity, purity, safety, chemical characteristics of the natural products required for pharmacological works leading to drug discovery and development.

(vii) Because its multidisciplinary characteristics, pharmacognosy is closely related to botany and phytochemistry and shares some grounds with biochemistry, physiology, enzymology, food technology, taxonomy, anatomy, morphology, phytochemistry, cultivation, and conservation of medicinal plants. Pharmacy is related to the majority of pure and applied science disciplines including some of these subjects.

2.4 History of Development of Pharmacognosy

The history of development of pharmacognosy is the history of gradual advancement in use of plants and other products of natural resources for therapeutic purposes. From antiquity until the availability of medicaments as pure chemicals and synthetic drugs in nineteenth century, people were completely dependent on crude drugs from medicinal herbs and other natural sources for prevention and treatment of their ailments. Many herbs and spices were historically used by humans to season food and to combat food-borne pathogens, and therefore, the history of herbalism overlaps with food history (Billing and Sherman 1998; Lai and Roy 2004; Tapsell et al. 2006). Pharmacognosy began in ancient times with the search for the natural medicaments including plants, animals, and minerals from the surrounding environment, and so it was linked with the healthcare activities of the most primitive human race of the remote past. Healing herbs and other natural elements existed long before the existence of people on earth, and they had only discovered their curative power. There are historic sites in Iraq that show Neanderthals used yarrow, marshmallow, groundsel, centaury, ephedra, muscary, etc., herbs more than 60,000 years ago. The people of early days tried to alleviate their sufferings or illness by using plants as medicaments plants that were growing in the surroundings, and their innovation of medicinal properties of plants was not based on any scientific method or on the knowledge of chemical constitutes of plants. The ancient people exploration of medicinal properties of plants throughout the ages discovered crude drugs and acquired knowledge of pharmacognosy in many ways including trial-and-error guesswork, observation, accidental discovery, curiosity, search for food, etc. (Photographs 2.2, 2.3, 2.4, 2.5, 2.6).

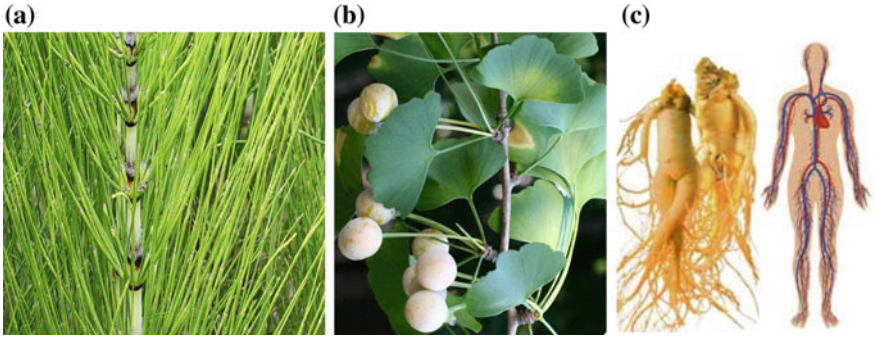
i. Trial-and-error guesswork: Trial-and-error guesswork means that try and then discard the object until it serves the purpose. This method helped ancient people to distinguish between the beneficial and poisonous plants. This was a rough and time-consuming method of identifying herbs; people used this method when they were nomad and lived on hunting wild animals and gathering plants from the wild. There would be a long and flat learning curve, and they might had innumerable mistakes and problems to identify toxic, edible, and curative fruits, seeds, tuber, etc., gathered from the wild. Ancient people led by instinct, taste, experience, and wisdom used plants for healing. They dug, dried, chewed, pounded, rubbed, and brewed many of the plants surrounding them and tried to discover herbal effects through trial-and-error guesswork. They discovered that some plants were good for food, some were poisonous, and some produced bodily changes such as increased perspiration, bowel movement, urination, relief of pain, hallucination, and healing. Development of a number of innovative techniques, computer-based technology, and biomathematical models in the recent years has replaced the inefficient age-old trial-and-error guesswork method of drug discovery.



Photograph 2.2 **a** Kalanchoe pinnata (*Bryophyllum pinnatum*, Pathorcuchi); an age-old drug for diabetic patient, **b** Rosemary (*Rosmarinus officinalis*) used for medicinal purposes by prehistoric peoples

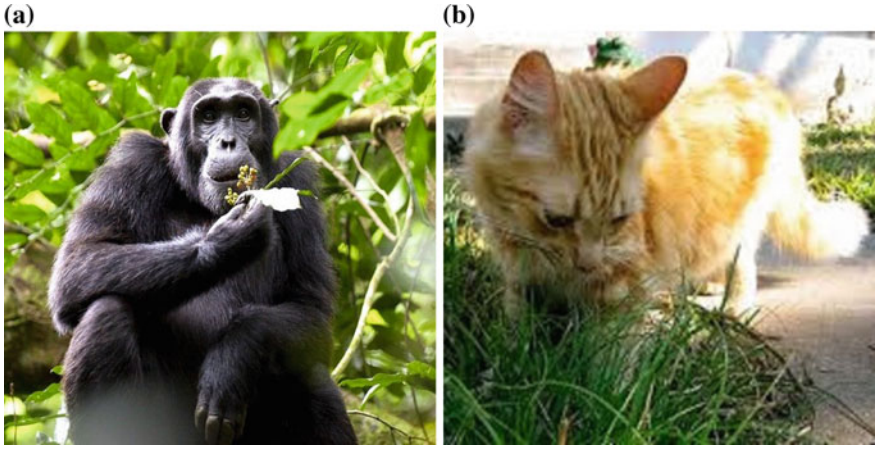
ii. While searching for food: Many of the herbs and spices used by humans were identified, while they were searching for food plants, and as time went by, they discovered the therapeutic benefits of herbs and spices. Food such as meats was stored with the help of herbs in the prehistoric households, and today, the same plants are used as culinary spices. Herbs or medicinal plants and spices are used to produce natural conservatives. Some of the commonly used herbs and species used today for food preservation are: cinnamon, clove, ginger, oregano, pepper, rosemary, sage, thyme, turmeric, etc. Recently, scientists from Aarhus University, Denmark, in collaboration with the Danish Meat Research Institute produced a new method of preserving meat with herbs and berries like aronia (chokeberry), sage, savory, sloe (blackthorn), lingo berry, wild garlic (ramsons), red currant, and horseradish (Benson 2012). Spices and herbs have been used for thousands of centuries by many cultures to enhance the flavor and aroma of foods. Early cultures also recognized the value of using spices and herbs in preserving foods and for their medicinal value. Since the late nineteenth century, scientific experiments have documented the antimicrobial properties of many spices, herbs, and their components (Shelef 1983; Zaika 1988). The ancient people were not aware of this quality of their collected herbs and spices, but they discovered the properties through repeated use.

Photograph 2.3 **a** Apple and tomato as food items are rich source vitamins, minerals, and antioxidants; **b** thyme herbs; and **c** spices such as parsley, basil, oregano, garlic, turmeric, pepper possess antimicrobial properties



Photograph 2.4 Prehistoric signature plants: **a** horsetail, **b** ginkgo (leaves and fruits), and **c** ginseng roots show resemblance with human anatomy

iii. Signature of nature: Many naturally growing plants or their parts show some superficial resemblances with human anatomy. The ancient people might have put emphasis on definite 'signatures' resemblance between plant and ill organ,



Photograph 2.5 **a** Common chimpanzee (*Pan troglodytes*) taking *Aspilia* sp. to fight intestinal parasite; **b** a cat eating grass—these are examples of zoopharmacognosy. *Source* iStockphoto.com

while they were searching and selecting plants for therapeutic use. Such superficial structural similarities were the selection criteria for curative use. horsetail, gingko, ginseng, etc., are ancient signature plants.

Belief in this concept was developed independently among different cultures in ancient times. Later on, it became popular as 'Doctrine of Signature.' The Doctrine of Signatures has probably existed as long as people have looked at plants. Configuration and structure of a plant guided early man to its use in the treatment of different diseases, e.g., horsetail mimics cartilage, and was thought to support the connective tissue, leaves; the cross section of the fruit of the *Ginkgo biloba* resembles a brain and, today, *Ginkgo* is used for memory loss; ginseng root resembles human body and has been used for thousands of years as a tonic for the entire body.

iv. Animal's instinctive discrimination between toxic and palatable plants. Animals survive in a highly complex, dynamic, and unpredictable habitat, and they can instinctively discrimination between toxic and palatable plants. Ancient people after a closer look on animal's behavior found that sick animals were using certain herbs that they normally ignore. Intimate and careful observation of such instinctive behavior of animals was helpful for ancient people in choosing the beneficial plants from medicinal point of view. Later, they were incorporated into prehistoric shamanism and then into medicine. Growing scientific evidence supports the view that wild animals have knowledge for self-medication, e.g., chimpanzees eating *Aspilia* shrub and pith of *Veronia* plant to remove parasitic worms from the intestinal lining. Many other animals including birds, bees, cat, deer, dog, elephants, elk, lizards, and various carnivores are known to consume medicinal plants for self-medication (zoopharmacognosy). Scientists of the present time also use this method to isolate active compounds from medicinal plants.

Photograph 2.6 **a** *Terminalia arjuna.* (*a*) Tree trunk with split bark, (*b*) bark separated from the tree trunk, (*c*) bark in powder form (the drug in usable form) **b** *Cinchona pubescens* (Quinine) tree (*left*) and dry bark (*right*) (BioWeb Home, AGE Fotostock)

v. By accidental discovery or fortuitous accidents. The use of plants for medicinal purposes began in ancient times, and it is believed that some of these plants were accidentally discovered (unexpected discoveries by accident). The discovery of antimalarial drug (quinine) by a South American from Cinchona bark (known as quina-quina to indigenous people) and antibiotic penicillin from *Penicillium* mold happened accidentally. The accidental discoveries are referred to as drug serendipity (finding of one thing while looking for something else). There are many examples of serendipitous discoveries of medicinal plants and their constituents. Discovery of psychotropic medicine such as potassium bromide, chloral hydrate, lithium was serendipitous. The medicinal use of *Cannabis* is as old as about 5000 years or more, but the discovery of its medicinal applications of *Cannabis sativa* was accidental. It was a source of nutritious seeds for the ancient people, but later they noticed the dizzying side effects due to accidental intake of flower parts with the edible seeds. From accidental consumption, purposeful use developed and the earliest form of pharmacology began. Cannabis is a powerful medicinal plant famous for its psychotropic properties. Some of the most important modern discoveries in medicine, e.g., smallpox vaccine, insulin and its use in diabetes treatment, X-rays, Viagra, are serendipitous or accidental discovery.

In course of time, ancient people through their health-related and other activities acquired a considerable volume of knowledge about drug and drug application. Subsequently, a group of people emerged in each ancient community who acquired expertise in collecting, testing, and treating diseases. These people were the prehistoric or early 'Medicine Men.' They monopolized the knowledge of drugs and hide that knowledge in some mysterious incantations. They transferred this secret knowledge only to their trusted successors of the successive generations, who gradually increased the volume of knowledge about drugs and their uses. Initially, the transfer of the acquired knowledge from generation to generation was done verbally by the use of signs and symbols. As civilization progressed, transfer and recording of the knowledge were done in writing, e.g., clay tablets, papyrus. Throughout the Mesopotamian tablets and the Egyptian papyri, references are made to the medicinal use of cannabis as a remedy for acute pain, fever, trench foot/gout/sore feet, inflammation, gynecological disorders, colorectal illness, serosity, bacteria (Photograph 2.7).

The history of the use of medicinal plants for therapeutic purposes, i.e., the history of development of herbalism and pharmacognosy, passed different historical periods such as (i) prehistory, (ii) ancient history (Mesopotamia, Ancient Egypt, India, China, Ancient Greece and Rome), (iii) middle ages, (iv) early modern era (sixteenth to nineteenth century), and (v) modern era (from twentieth century onward). Historically, herbal medicine or herbalism belongs to four basic systems such as (i) traditional Chinese herbalism, (ii) Ayurvedic herbalism, (iii) Western herbalism (originated in Greece and Rome and spread to other parts of Europe and then to America), and (vi) Arab traditional medicine (Unani system of medicine).

Photograph 2.7 Sumerian medical tablet (2400 BC) listed 15 prescriptions (Library of Ashurbanipal) (*left*); Papyrus Ebers (1550 BC) (Antique Cannabis Book) (*right*). (https://rootsnwingz.com/tag/education/)

In addition to these, other forms of herbalism also exist in many parts of the world (e.g., Kampo medicine in Japan).

(i) Prehistory

Early records on medicine of natural origin from plants, animal parts, and minerals have been discovered from the ancient Babylonian, Egyptian, Indian, Chinese, North Africans, Geek, Roman, and Celt cultures. All early cultures had left valuable evidences in their past activities on therapeutic use of their plant resources. Prehistoric physical evidence of the use of herbal remedies of the remote past (60,000 years old) was found in a burial site of a Neanderthal man in 1960 in northern Iraq (Solecki 1975). An analysis of the soil around the human bones revealed extraordinary quantities of plant pollen of eight species including yarrow (Achillea), marshmallow (Althaea), groundsel (Senecio), cornflower or centaury (Centaurea), Ma Huang (Ephedra), and tassel (Muscary). Seven of these were medicinal plants which are still in use throughout the herbal world (Bensky and Gamble 1993). Shanidar IV flowers, due to their considerable medical activity, would be a purposeful selection of the Middle Paleolithic Shanidar Neanderthals (Lietava 1992). However, the purposeful inclusion medicinal plant along with corpse in the Shanidar cemetery has now been disputed seriously (Sommer 1999;

Pettitt 2002). The body of Otzi, the Iceman, frozen in the Otzal Alps for more than 5300 years, contained medicinal herbs. These herbs appear to have been used to treat the parasites found in his intestines. The analysis of coprolites (desiccated fecal remains) of prehistoric man for undigested remains (macroremains and pollen) is a widely used method to get prehistoric information about the dietary and medicinal usage of plants (Bryant 1974; Reinhard et al. 1991). Analytical results of the 40 coprolites for pollen content of Caldwell Cave demonstrated the prehistoric people used medicinal plants such as *Ephedra, Prosopis*, and *Larrea* as pollen tea to combat diarrheal disease (Holloway 1983).

(ii) Ancient history

Plants have been the mainstream material source for shelter, food, and medicine for the people of all ages. They identified their nourishing value and healing power. In course of time, people entered from Paleolithic to Neolithic period and during the new stone age (8000–5000 BC), the lake dwellers gathered hundreds of plants and initiated cultivation of many crop species including several with significant medicinal value (e.g., *Papaver, Sambucus, Fumaria*). The practice of early mind–body medicine was followed by the rise of Egyptians (2500 BC) rational medicine. After the discovery of formal writing systems, the ancient prehistoric people began documenting the history of use of medicinal plants. Thus, they entered into the historic time several thousand years ago. Development of trade routes enhanced the exchange of views and practices regarding the use of herbal medicine among the ancient cultures of different regions.

The Sumerian civilization in southern Mesopotamia began by 3500 BC, and the characteristic cuneiform writing developed around 3100 BC. Mesopotamian medical knowledge compiled as 'Treatise of medical diagnosis and prognoses,' written in cuneiform, was preserved in clay tablets for several hundred years in the library of Assurbanipal. The Sumerians created clay tablets with lists of hundreds of medicinal plants including myrrh, opium. The Babylonians were aware of the use of about 250 medicinal plants at about 3000 BC. The Babylonian medicine developed in Mesopotamia from 3000 BC to 1648 BC. Babylonians had two types of medical practitioners: the asipu (whose cures were said to be magical based on prayers, chants, and rituals to propitiate the angry gods) and the asu (whose cure were basically medical). The Babylonian society at that time believed in fearsome gods who used illness to punish people for their sins (sin was the cause of a patient's illness). Babylonian provides the earliest known record of practice of the art of apothecary (2600 BC), and the practitioners were three in one (priest, pharmacist, and physician). They described in clay tablets the symptoms, prescriptions, directions of compounding, and finally prayer to God. The Babylonian physicians utilized an extensive repertory of herbal medicines (e.g., cassia cinnamon, turmeric, garlic, myrtle, thyme, willow, pear, fir, fig, dates), salt as an antiseptic and saltpeter as astringent as well as animal products (e.g., milk, snake skin, turtle shell). The Babylonian Materia medica on a clay tablets is one of the oldest known medical treatises in existence, dated back from 2200 to 2100 BC. 'An infection without a

doctor is like hunger without food' is an old Babylonian proverb which signifies their habitual dependence on doctors to suit their needs just as peoples' dependence on food to suit hunger. They also used polished diorite in medical writings, e.g., the 'Law Code of Hammurabi (1700 BC), a medical document that demonstrates the skill of Mesopotamian physicians in the use of different herbal drugs including sesame oil, belladonna, henbane, licorice, mandrake, sinna, mint, poppy.

Like Mesopotamian, many ancient documents revealed that plants were used medicinally in China, India, Egypt, Greece and Rome, America, Australia, New Zealand, etc., long before the beginning of Christian era. In China, medicinal plants had been in use since 5000 BC. The Chinese pharmacopoeia, the 'Pen T'sao' written by Shen nung (3000 BC), appears to be the oldest pharmacopoeia on earth. It described 365 drugs (120 emperor, 120 minister, and 125 servant drugs) including the use of Chalmoogra (*Hydnocarpus kurzii*) seed oil against leprosy. Other medicinal plants included in this authoritative treatise were aconite (*Aconitum* spp.), ephedra (*Ephedra sinica*), hemp (*Cannabis sativa*), opium (*Papaver somniferum*), rhubarb (*Rheum rhabarbarum*), *Podophyllum*, ginseng (*Panax* spp.), stramonium (*Datura stramonium*), cinnamon bark (*Cinnamomum* spp.), etc., and these are still recognized in pharmacy. The ancient Chinese doctors are now regarded as pioneer in the use of herbal preparations. The other earliest medical treatises of China include inscription on oracle bones from the Shang dynasty (1766–1122 BC) and medical treatises on silk banner and bamboo slips. The 'Shang Hang Lun' (treatise on the treatment of acute diseases caused by cold) of Chang Chung Ching (142–220 AD) along with 'Chin Kuei Yao Lueh' (prescription from the golden chamber) comprises the basis of Chinese and Japanese herbalism (Kampo). Tao Hong Jing (456–536 AD) compiled 'Pen T'sao Jing Ji Zhu' (commentaries on the herbal classic) which contained 730 herbs of six categories such as minerals, grasses and trees, insects and animals, fruits and vegetables, grains. During Sui dynasty (589–618 AD), specialized books ('Sui Shu Jing JiZhi'—bibliography of the history of Sui) on herbal medicine include their cultivation ('Zhong Zhi Yue Fa'—how to cultivate herbs?) and collection from the wild ('Ru CaiYue Fa'—how to collect herbs in the forest?). Pharmaceutical system was established in China during Sung dynasty (960–1276 AD). Li Shi Zhen (1518–1593 AD) compiled and completed 'Pen T'sao Kan Mu' (herbal with commentary) in 1578 during dynasty. This book listed 1892 drugs and over 11,000 prescriptions.

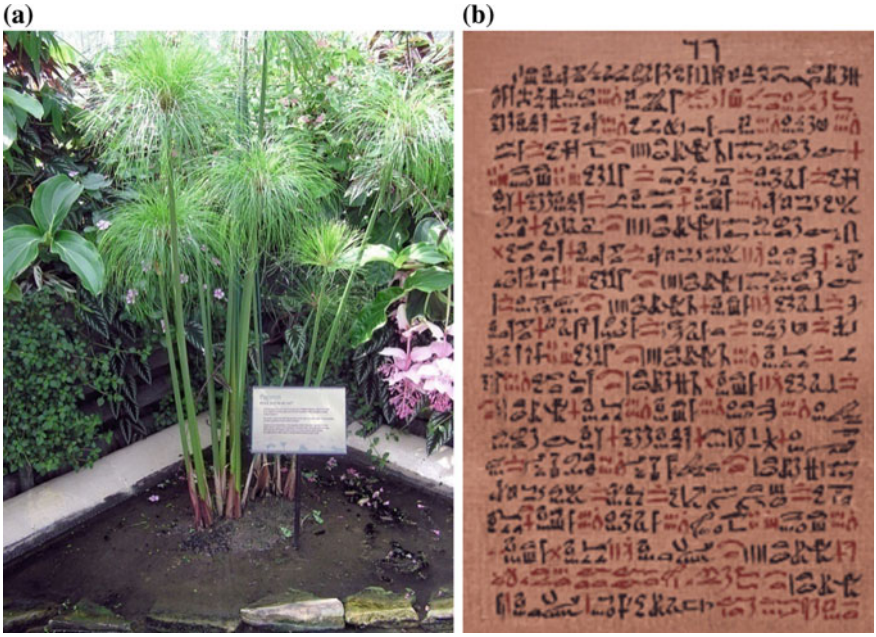
Among the ancient civilizations, Indian subcontinent has been known to be rich repository of medicinal plants. About 8000 herbal remedies have been codified in Ayurveda (Ayur means life, veda means the study of, i.e., life, knowledge), the medicine of classical antiquity. Ayurveda developed significantly during the Vedic period based on four Vedas (e.g., the Rig, the Sama, the Yajur, and the Atharva Vedas) of Hinduism compiled/written in Sanskrit ancient time between 6000 and 4000 BC. Out of them, the Rig Veda (the oldest written book preserved in the library) and Atharva Veda represent some of the earliest available written documents about the medical knowledge and practices that formed the basis of the Ayurveda system. The Rig Veda contained description of 67 species of medicinal plants, Yajur Veda 81 species and Atharva Vaveda 290 species. Charak Samhita

and Sushrut Samhita had described properties and uses of 1100 and 1270 species, respectively. The Charaka Samhita, the Sushruta Samhita, and the Astanga Sangraha are the greater triad and constitute important text in Ayurveda written by the three great authors—Charaka, Sushruta, and Vagbhata, respectively. Many herbs (700), minerals (64), and animal preparations (57) used in Ayurveda were later described in Sushruta Samhita.

A holistic approach is followed during diagnosis and therapy, and it is fundamental to Ayurveda. The earliest plant medicines used in the Ayurvedic system were described around 1200 BC, and these are still in use in the classical formulations. By the medieval period, Ayurvedic practitioners developed a number of medicinal preparations and surgical procedures for the treatment of various ailments. Practices that are derived from Ayurvedic medicine are regarded as part of complementary and alternative medicine. At present, Ayurveda is well integrated into the Indian national healthcare system following the establishment of state hospitals for Ayurveda in different parts of the country.

The ancient Egyptians left their medical procedures and practices as written document on papyrus. Papyrus is a thick type of paper made from the pith of the papyrus plant (*Cyperus papyrus*), and its use as a writing material goes back to antiquity (Photograph 2.8). The papyri texts described in detail the medical procedures and practices including herbal remedies, surgery, and a mixture of magic and religious spell. So far nine principal medical papyri are known, and they were named after their original owners (Edwin Smith, Chester Beatty, Carlsberg), the site of their discovery (Kahoun, Ramesseum), the towns where they were kept (Leyden, London, Berlin) or their editor (Ebers).

The Ebers Papyrus or Papyrus Ebers (1550 BC) named after Georg Ebers, a German Egyptologist, that includes medicine, obstetrics, gynecology, and surgery; Edwin Smith papyrus or Edwin Smith Surgical Papyrus (1600 BC)—the oldest known surgical treatise on trauma; Kahun medical papyrus (1900 BC) that includes medicine, obstetrics, gynecology, pediatrics, and veterinary medicine, are some of the oldest and most important medical papyri of ancient Egypt. It is believed that these papyri have been copied from earlier texts, perhaps dating as far back as 3400 BC. They represent the Egyptian oldest medical document. The Ebers papyrus, discovered in 1862, contains around 876 prescriptions made up of more than 500 different substances. It is a collection of diverse medical texts that offers the most complete record of Egyptian medicine. The scroll addressed ailments ranging from crocodile bites to toenail pains contains a 'treatise on the heart,' chapters on contraception, diagnosis of pregnancy, birth control and other gynecological matters, intestinal disease and parasites, helminthiasis, hookworm, filariasis, ophthalmology, dermatology, obstetrics, dentistry and the surgical treatment of abscesses and tumors, bonesetting and burns, diabetes mellitus, trachoma, arthritis, and a short section on psychiatry as well as despondency. It also includes an accurate description of the circulatory system, noting the existence of blood vessels throughout the body, and the hearts function as a center of the blood supply. The Edwin Smith papyrus contains surgical instructions and formulae for cosmetics. The Kahun Gynecological papyrus narrates about the health of women and birth



Photograph 2.8 **a** Papyrus plant (*Cyperus papyrus*) at Kew Gardens, London (https://en.wikipedia.org/wiki/Papyrus#/media/File:Kew.gardens.papyrus.plant.arp.jpg); **b** The Ebers papyrus suggests treatment for asthma: a mixture of herbs heated on a brick to produce fumes for inhalation (https://en.wikipedia.org/wiki/Ebers_Papyrus)

instructions. Ramesseum medical papyri (1800 BC) include medicine, gynecology, ophthalmology, rheumatology, and pediatrics; Hearst papyrus (2000 BC) includes urology, medicine, and bites; London medical papyrus (1300) includes skin complaints, eye complaints, bleeding, miscarriage, and burns; Brugsch medical papyrus (1350–1200 BC) and Carlsberg papyri include obstetrics and gynecology, medicine, pediatrics, and ophthalmology; Chester Beatty medical papyrus (1200) includes headache and anorectal disorders, etc., are some other worthy mentionable papyri.

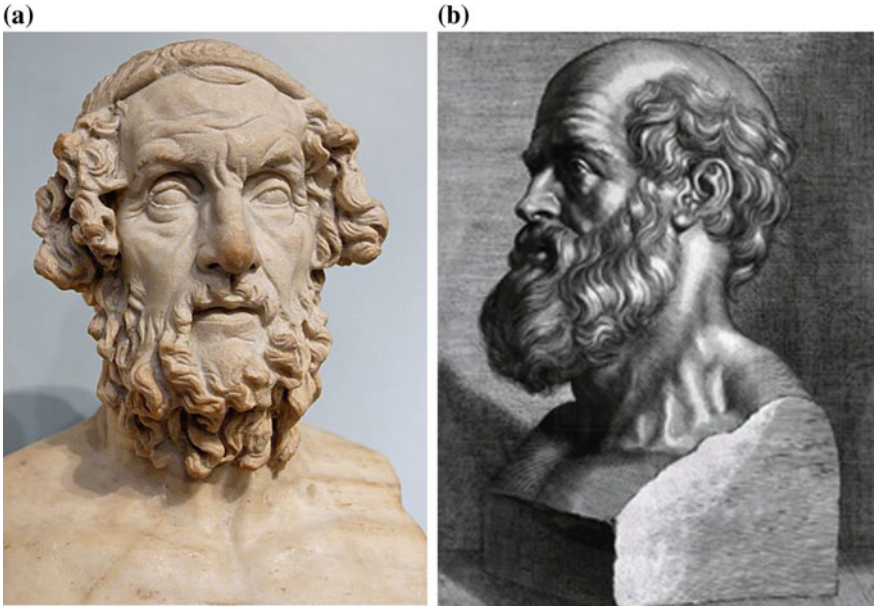
The Egyptian papyri listed ailments and their treatments, ranging from disease of the limbs to diseases of the skin and recorded names and properties of hundreds of medicinal plants including alkanet (*Alkanna tinctoria*), aloe (*Aloe vera*), ammi (*Ammi majus*), bayberry (*Myrica gale*), elderberry (*Sambucus nigra*), cannabis (*Cannabis sativa*), caraway (*Carum carvi*), cassia gum (*Cassia obtusifolia*), ceder (*Cedrus libani*), coriander (*Coriandrum sativum*), cumin (*Cuminum cyminum*), cyperus (*Cyperus rotundus*), fennel (*Foeniculum vulgare*), flax (*Linum usitatissimum*), hemlock (*Conium maculatum*), juniper (*Juniperus* spp.), lotus (*Nelumbo nucifera*), mandrake (*Mandragora officinarum*), myrrh (*Commiphora myrrha*), nasturtium (*Nasturtium officinale*), onion (*Allium cepa*), garlic (*Allium sativum*), oak gall or oak apple, opium (*Papaver somniferum*), papyrus (*Cyperus papyrus*),

peppermint (*Mentha* × *piperita*), pomegranate (*Punica granatum*), ricinusbean (*Ricinus communis*), saffron (*Crocus sativus*), senna (*Senna alexandrina*), turpentine, thyme (*Thymus vulgaris*), henbane (*Hyoscyamus niger*), wheat (*Triticum aestivum*), wild lettuce (*Lactuca virosa*), ziziphus (*Ziziphus jujube*), many essential oils, bile, lard.

A diet rich in radish, garlic, and onion was preferred for workers in Egypt, and modern scientific research showed these items are rich in powerful natural antibiotics such as raphanin, allicin, and allistatin, respectively. They used honey as excellent antiseptic, willow in toothache, mint in gastric ailments, pomegranate against parasitic worms—'snakes' of the digestive system—moldy bread as antibiotic, etc., and left huge information about the use of medicines and herbs. Ancient Egyptian physicians earned expertise in performing eye surgery, to suture wound, wound healing, stimulation of blood production, curing night-blindness by feeding the patient vitamin A rich powdered liver, and they adopted an ethical code centuries before the Hippocratic Oath. It is thought that the Egyptian herbals were enriched from the translation of ancient texts, and trade and politics carried the Egyptian tradition to other regions of the world. So far, the level of medical knowledge and sophistication is concerned; the physician of ancient Egyptian outstripped both the Roman and Greek physicians and they were unparalleled until the golden age of Islam.

Medicinal knowledge about the ancient Greek mostly comes from Homer (Photograph 2.9a) and his epicpoems. Homerin his epics 'the Iliad and the Odyssey,' written in about 800 BC, served as textual sources of Greek medicine before the time of Hippocrates (470–410 BC) when there was no published medical text. While narrating the medical care of warriors, Homer, in his poems cast light on the ancient Greek medical knowledge and practices, descriptions of injury, disease treatment, and human anatomy at that time. Homer described a few warriors (e.g., Machaon) who were specialists in the art of healing with the use of herbal remedies, bandages, and wine. The ancient Greeks regarded illness as a divine punishment and healing as a gift from the gods, and by the 500 BC, they tried to acknowledge the material causes for illnesses and moved toward scientific enquiry leading to the exploration of connection between causes and effects, symptoms of illness, and success or failure of various treatments. From this simple initiative, Greek medicine rapidly developed over the course of the next several centuries.

Ancient Greece as well as Rome and Egypt played significant role in medical history. The Greek borrowed much of their medical knowledge from the ancient Egypt, and they also developed their own skills that definitely influenced the history of Western medicine. Many of the founders of the ancient Greek schools of medicine earned their knowledge in medicine from Egyptian priest doctors. The practice of medicine using medicinal plants flourished most during the Greek civilization. Some of the early Greek naturalists, scientists, and physicians who contributed enormously to the development of human knowledge about medicinal plants are Hippocrates (460–370 BC), Aristotle (384–322 BC), Theophrastus (370–287 BC), Dioscorides (first century AD), Pliny the Elder (23–70 AD), and others. The Unani (Greco-Arabic) system of medicine, improved by the Arabs, owes its



Photograph 2.9 **a** Homer (https://commons.wikimedia.org/wiki/File:Bust_Homer_BM_1825.jpg). 2.87″ × 2.12″. **b** Hippocrates Bust (Public Domain) https://explorable.com/ancient-medicine 2.88″ × 218″

origin to Greece. The theoretical framework of *Unani* medicine was based on the teachings of Hippocrates (460–377 BC). Hippocrates of Kos, the father of medicine, freed medicine from superstition and philosophic speculation, elevated it to a level of science by putting emphasis objective observation and critical deductive reasoning (Fig. 6.9b). Thus, he laid down the scientific basis of drug use from the abuse of prejudice. The Hippocratic Corpus serves as a collection of texts including medical teaching, recipes, and remedies, but some of its authorship is disputed. Hippocrates was taught under Egyptian priest-doctors, and the treasure of the ancient Greek school of medicine was enriched by the knowledge he borrowed from the Egyptians. He wrote a treatise of about 300–400 medicinal plants including mint (*Mentha spicata*), opium (*Papaver somniferum*), rosemary (*Rosmarinus officinalis*), sage (*Salvia officinalis*), and verbena (*Verbena officinalis*). Ancient Greek medicine was centered on the humor theory, and Hippocrates believed in four bodily humors (blood, yellow bile, black bile, and phlegm) and in the causes of disease from their imbalance. He, however, believed in the glandular secretory origin humors and their imbalance due to outside factors and put emphasis on appropriate diet and hygienic measures for disease improvement. Greek herbal medicines were mostly based around restoring the balance of humors, and this belief continued in European thought until middle Ages. Greek medicine up held the concept 'Medicatrix Naturae,' i.e., 'Mother Nature is a healing goddess and remedies of all diseases are to be found in the biosphere.' Ecology supports the

view, and the animal kingdom and all sentient beings depend on nature (the plant) for food, medicine, and fresh air. Hippocrates used herbs in treatment, and his teaching was 'Let your food be your medicine and your medicine your food.' Hippocrates used both local and imported herbs from Arabia.

Aristotle, a philosopher, recorded the properties of more than 500 plants of medicinal importance. Theophrastus (370–285 BC), the father of botany, wrote De Historia Plantarum (Plant History) and De Causis Plantarum (Plant Etiology) with many kinds of plants (>500) including cinnamon, iris rhizome, false hellebore, mint, pomegranate, cardamom, fragrant hellebore, monskhood, and their medicinal use as well as culture. 'Historia Plantarum,' the first systematization of the botanical world, was remaining equally important for herbalists and botanists for centuries after Theophrastus. Krateus ($\sim$100 BC) is a Greek herbalist who produced an illustrated work on medicinal plants (a pharmacological book for medicinal plants). His influence is felt in the De Materia Medica of Dioscorides and in other works. Dioscorides, the father of pharmacognosy, was a military physician and pharmacognosist of Roman army, and he studied medicinal plants wherever he travelled with the army. He published five volumes of a book on pharmacopeia, entitled 'De Materia Medica' in 78 AD. This encyclopedic work described more than 600 medicinal plants including their name and synonym with picture, habitats, botanical description, drug properties, medicinal use, collection and storage instructions, adulteration and methods of detection, veterinary uses. Like Eber papyrus, this work also contained a number of recipes and prescriptions for ailments and among, and there were 80% plant, about 10% minerals, and 10% animal medicines. It was a significant herbal designed for practical purposes and was used widely utilized throughout the ancient period for over 1600 years. De Materia Medica was considered to be the authoritative source of pharmacological information (pharmacopoeia) until the late middle Ages and the Renaissance.

Diocles of Carystus, a new pupil of Aristotle, wrote extensively on herbalism and treatment, and because of his high prestige, he would be referred to as 'the second Hippocrates.' His original texts no longer exist, but many medical scholars such as Galen, Celsus, Soranus, and others quoted Diocles extensively. Pliny de Elder (23–79 AD), a contemporary of Dioscorides, wrote 'Historia naturalis' (Natural History)—an encyclopedic text, a comprehensive guide to nature, and the largest compilation on medicinally valuable plants (>1000) from the Roman period. The Greeks had developed expertise in surgery, and the equipment they used includes forceps, scalpels, tooth-extraction forceps, catheters, and syringes for drawing pus from wounds. These are also recognizable today. They acquired the art of splinting and treating bone fractures and adding compresses to prevent infection. The Greeks together with the Egyptians lay at the root of the modern history of medicine, understanding the value of cleanliness, medicines, and the finer arts of surgery. Their knowledge passed down to the Romans, who preserved the medical skills and refined them.

The Roman contributed a lot to the development of medicine, especially the preventative medicine. They recognized the role of dirt and poor hygiene in spreading disease, and their engineering skill ensured clean water and installed

elaborate sewage systems. The Roman military surgeons developed into fine practitioners of their art, and under their treatment, the Roman soldiers had a much lower chance of dying from infection than those in other armies. Galen (131–200 AD), a Greek physician, surgeon, and philosopher who worked in Rome, is the most illustrious name in the history of Roman medicine. Galen wrote many texts regarding herbs and their properties, and the most notable one was 'Works of Therapeutics' aimed to combine all branches within medicine to restore health and prevent disease. While the subject of therapeutics encompasses a wide array of topics, Galen's extensive work in the humors and four basic qualities helped pharmacists to better calibrate their remedies for the individual person and their unique symptoms. He practiced and taught both pharmacy and medicine and wrote many texts ($\sim$600 treatises) on many aspects of medicine, including herbs and their properties, physiology and anatomy, pharmacy, hygiene, etiology, semeiotics as well as therapeutics, and described hundreds of recipes and formulations containing ingredients of medicinal plants and animal origin. His principle of preparing and compounding medicines, 'Galencial pharmacy,' dominated the western world for over 1500 years. The idea of Galen formed the basis of both allopathic and homeopathic systems of medicine practiced today (Sofowora 1982). Pharmacognosy progressed gradually and formed the basis and beginning of both pharmacy and medicine.

(iii) Middle Ages

The long period between ancient Greek and Roman cultures and the Renaissance a may be designated as middle ages. During this period, several schools of medicine were developed that ensured the progression of herbalism. There were three major sources of information on medicine and medical practices such as (i) Arabian School, (ii) Anglo-Saxon Leechcraft, and (iii) Salerno. The Spanish Muslim botanists (e.g., Al-Ghafiqi, Ibn Al-Awwan, and others) made the greatest contribution in botany, advanced botany beyond Dioscordes, and augmented herbology by addition of 2000 plants and botany reached its zenith in Spain of medieval times. They established botanical gardens in Cordova, Baghdad, Cairo, and Fez for teaching and experimental purposes. Ibn-Al-Baytar (1148–1197 AD) was a great botanist and pharmacognosist of Spain of medieval times and ranked with Dioscorides in that respect. He described >1400 drugs and wrote two medicinal compendium, e.g., Al Mughani-fial Adwiyah al-Mufradah and Al-Jami Ji al Adwiyah al Mufrada where he arranged plants collected mostly from Spain and North Africa in alphabetic order and gave instructions regarding preparation of the drug, administration, purpose, and dosage for each plant.

The two great Persian Muslim physicians Al-Razi (850–925 AD) and Ibn Sina (980–1037 AD) constructed an imposing edifice in the Islamic era. These two scientists by enriching the original Greek system of medicine laid down the foundation stone of modern Western medicine. Al-Razi and Ibn Sina are ever remembered for their famous books 'Kitab al-Mansuri' and 'Al-Kanun,' respectively, and they were used as important textbooks throughout Europe until the

Photograph 2.10 Dioscorides' Materia Medica, copy in Arabic, describes medicinal features of cumin and dill. *Source* https://en.wikipedia.org/wiki/File:Arabicherbalmedicine_guidebook.jpeg

sixteenth–seventeenth centuries. The Al-Kanun of Ibn Sina was known for its systematic experimentation, physiological study, discovery of infectious and sexually transmitted diseases, quarantine method to limit the spread of infectious diseases, experimental medicine, clinical trials, and method of diagnosis of diseases. It includes descriptions of some 760 medicinal plants and their related medicine. Ibn Altabari (770–850 AD), Al Zahrawi (930–1013), Ibn Al Haitham (960–1040), Ibn al-Nafis (1213–1288), Ibn Khaldun (1332–1395), and many other Arabs were famous for their contribution toward the development of herbal medicine in the middle ages. The Arab physicians used aloe, anise, basil, camphor, cinnamon, cloves, coffee, coriander, cucuma, deadly nightshade, fennel, ginger, henbane, licorice, myrrh, nutmeg, syrups, juleps, oregano, pepper, rheum, rosemary, senna, strychnos, saffron, thyme, and many other. They replaced drugs with strong action by drugs with mild action (e.g., *Sennae folium*, a mild laxative, was used to replace *Helleborus odorus*). Based on the Greek system, the ancient Arab physicians contributed enormously to the development of modern medicine (Photograph 2.10). The Muslims were the first to establish hospitals, dispensaries, pharmacopoeia, and medical schools in the world.

'Herbariun Apuleius' is a famous manuscript of Anglo-Saxon medicine (480–1050 AD). It contains recipes and uses of >100 herbs. Leech means medical practitioner, and 'The Leech Book of Bald' (925 AD), the oldest surviving herbal of the West, contains many formulae and herbal remedies, but over shadowed by superstitious notations. Wood-Betoney, Vervain, Mugwort, Plantain, Yarrow, etc., were the most used herbs of the Saxon times. 'Physicians of Myddvai' (1250) contains the artful herbal practice of the family Myddvai.

Salerno, a famous school of health science and medicine in Italy, was founded by Charles the Great (742 AD–814). Constantine the African, a student of the school, epitomized (i.e., abridged) the Western medicine with Arab medicine, and in fact, he introduced Arabian medicine into Europe. 'Experiments of Cohpon' and 'Regimen Sanitatis Salerni' were two famous books. During the early middle ages, the Western knowledge of pharmacy and medicine was preserved in the monasteries. The monastic works were mainly translation and carbon copy of the ancient Greco-Roman and Arabic works. The monks gathered herbs from the wild or raised them in their own herb gardens (including sage, sea onion, iris, mint, common centaury, poppy, marsh mallow). Sage (*Salvia officinalis* L.) was a mandatory plant in all Catholic monasteries and prepared medicine according to the art of apothecary for the sick and injured persons. Following renaissance in Europe when new political independence was achieved from the church, many great herbals were written, compiled, and printed (e.g., Herbals of Brunfels, Bock, Fuchs, Mattiali).

Brunfels (1488–1534 AD) in his original work in botany arranged herbs in alphabetic order with illustrations. Bock (1498–1554 AD) continued the work of Brunfels in a very scientific way classified for the first time into herbs, shrubs, and trees and laid the foundation of Linnaeus. He clearly described the plants in his herbal and thus developed the prototype of phytography. Fuchs (1501–1577 AD) added to his herbal at least 100 new plants that were not mentioned earlier in the works of Dioscorides, Pliny, and Galen. Mattioli (1500–1577 AD) was a famous herbalist of the sixteenth century and incorporated many New World plants in his herbals.

Paracleus (1493–1541), a well-known German alchemist and herbalist of the medieval age, presented the idea of the 'Doctrine of Signatures,' and it had been an idea of herbalists for centuries. The 'Doctrine of Signatures' in simple terms is the idea that God has created everything with a sign (signature) and the sign was an indication of the purpose for the creation of the item. By observation, one can determine from the color of the flowers or roots, the shape of the leaves, the place of growing, or other signatures, what the plant's purpose was in God's plan. According to this doctrine, symptoms of diseases or diseased organs reveal close resemblance with the herbal resources. For example, ginseng (*Panax ginseng*) root was suggested as tonic for good health as it resembled human figure, blue cohosh (*Caulophyllum thallictroides*) for muscular spasm treatment as its branches resembled limbs in spasm, blood red (*Sanguinaria cnadensis*) root sap for blood purification, stomach-shaped flower of lobelia (*Lobelia inflate*) for emetic purpose, yellow-green juice of the root of golden seal (*Hydrastis canadensis*) for jaundice

treatment, walnuts for brain disorders, three-lobed liver shaped leaf of hepatica (*Hepatica acutiloba*) (liver leaf) liver ailments.

Paracleus idea was very much influential, and as a professor of medicine at the University of Basel, he refused to accept the classical medical books of Theophrastus, Galen, Dioscorides, Avicenna, and all others except Hippocrates. The 'Doctrine of Signatures' was highly developed during the European Renaissance, and it expounded in medical texts from the middle of the sixteen century right up to the end of the nineteenth century. Idea of the 'Doctrine of Signatures' by Paracleus was obviously wrong. Long before Paracleus, signature plants were probably first recognized in ancient China, where there was a classification that correlated plant features to human organs, e.g., yellow and sweet = spleen, red and bitter = heart, green and sour = liver, and black and salty = lungs.

Many vernacular names of temperate plants tell us how plants were once used to cure human ailments. Flowers shaped like a butterfly became cures for insect bites; liverwort relieves liver trouble, snakeroot, antidote for snake venom; adder's tongue cures wounds and inflammation from snake bite; lungwort cures pulmonary diseases; bloodroot cures blood disorders; toothwort relieves toothache; gravel wort dissolves stones in the urinary tract; wormwood expels intestinal parasites; pilewort cures hemorrhoids; mandrake promotes sexual passion in females; black-eye root removes bruise discoloration; maidenhair fern cures baldness. Long-lived plants were used to lengthen a person's life, and plants with rough stems and leaves were believed effective to heal diseases that destroy the smoothness of the skin, and roots with jointed appearance were the antidote for scorpion bites. Some of these were proved to be useful, and it was followed in Europe for long time (Murray 1995).

The medieval world (fifth to fifteenth century BC) was characterized by the expansion book culture. Translation is well-documented, began in Baghdad as early as eighth century, and expanded throughout European Mediterranean centers by the eleventh and twelfth centuries (Hoffman 2012). It was a collaborative effort, provided numerous versions and compilations of individual manuscript from diverse sources, and contributed great to science in the middle ages. The monastic works were mainly translation and hand copying of the ancient Greco-Roman and Arabic herbal literature and preserved these works in the monasteries; thus, they grew as local centers of medical knowledge. The monasteries were well known for their translation works from the ancient Greco-Roman and Arabic herbal literature. They developed in-depth herbal knowledge, grew the useful herbs in the monastic gardens, and treated various human ailments. Folk medicine at that time was practiced by herbalists, 'wise-women,' and 'wise men,' along with spells, enchantments, divination, advice, etc. Unfortunately, they often became the targets of the witch hysteria during the Dark Ages in Europe. Hildegard of Bingen, a twelfth-century Benedictine nun and famous women in the herbal tradition, wrote a medical text 'Causae et Curae' (Ramos-e-Silva 1999; Truitt 2009). The beginning of modern medical education could be linked with monastic works of middle ages (Krebs 2004).

(iv) Early modern era (sixteenth to nineteenth century)

The early modern era is extended from sixteenth to nineteenth centuries. The sixteenth and seventeenth centuries were the great age of herbals, and many of the books became available for the first time in English and other languages rather than Latin or Greek. During the eighteenth and nineteenth centuries, more plant America were incorporated and notable advancement of modern medicine began.

'The Grete Herball' appeared to be the first published herbal in English in 1526, and 'General History of Plants' (1597) and 'The English Physician Enlarged' (1653) of John Gerard and Nicholas Culpeper, respectively, were other two books. The best two herbals in English (e.g., The Herball, Gerard's text) were pirated translation. The blend of traditional medicine with astrology, magic, and folklore by Culpepper was ridiculous. Exploration and the Columbian Exchange introduced new medicinal plants to Europe. 'The Badianus Manuscript,' written in Nahuatl and Latin, was an illustrated Mexican herbal of sixteenth century (Gimmel 2008).

The second millennium, however, also saw the beginning of a slow erosion of the pre-eminent position of herbal agents as sources of therapeutic effects began to decline slowly in next century, and later on, Paracelsus introduced the use of chemical drugs such as arsenic, copper sulfate, iron, mercury, sulfur minerals. During the eighteenth century, Swedish botanist, taxonomist Linnaeus wrote numerous theses including *Medicamenta graveolentia* (Drugs with a strong smell), *Sapor medicamentorum* (The taste of drugs), *De methodo investigandi vires medicamentorum chemica* (regarding the chemical method to investigate the virtues of drugs), and *Ineberiantia* (Intoxicants). Linnaeus published *Materia Medica* in 1749, where he combined botany with medicine with an intension to explore the medical potential of nature.

In eighteenth century, herbal knowledge in the Americas was based on books including almanacs, Dodoens' New Herbal, Edinburgh New Dispensatory, Buchan's Domestic Medicine, etc., and the Native Americans shared some of their knowledge with colonists. In nineteenth century, formalization of pharmacology took place and people began to understand the specific drug action. Samuel Thompson and Thompsonians were very influential at that time.

A vast body of Greco-Roman knowledge of herbs was preserved and enlarged upon by the Arabs. This knowledge, much of which had been lost to Europe in the Dark Ages, was reintroduced to Europe when the Crusaders returned from the Middle East. In India too, traditional medicine incorporated a large number of herbal remedies; the Indian Materia Medica, published in 1908, listed 2982 medicinal plants. The knowledge developed on herbal medicine was transmitted at one time orally, and the earliest written form was the Egyptian papyri (1600 BC). This was followed gradually by clay tablets, parchments, manuscript herbals, printed herbals, pharmacopoeias, and books on the method of preparation of herbal medicine and recently by computerized information database systems. *De Materia Medica* (78 AD) is a pharcopoeia, an authoritative book on botanical medicine and pioneer of all modern pharcopoeias. It contained information of about 600 medicinal plants.

The use of medicinal plants by the people of other continents, especially the South America and Australian aborigines, enriched the world herbal knowledge. In fourteenth and fifteenth centuries, the medicinal plants like coca (*Erythroxylum* sp.) and tobacco (*Nicotiana tabacum*) were in common use in Latin American countries. European immigrants to North America during eighteenth to nineteenth centuries discovered that the indigenous Red Indian population was skilled at using the native plants as medicines and they began to incorporate them into their own remedies. Many of these new herbal remedies from the Americas were also brought back to Europe.

Greek civilization witnessed a highly developed system of medicine which used medicinal plants and minerals. Arab Muslims further enriched this system and developed the Greco-Arabic or Unani system, which formed the basis of modern Allopathic system of medicine. In the nineteenth century, the term 'materia medica' was used for the subject pharmacognosy.

J.A. Schmidt (1759–1809) of Austria introduced 'pharmacognosy' for the first time in a manuscript published posthumously in 1811, and C.A. Seydler of German used the term in his book in 1815 to include drugs of plant origin. The progress achieved during eighteenth and nineteenth century in the field of botanical sciences had a direct influence in pharmacognosy. The modern era after the nineteenth century was dominated by the single-component synthetic drugs pushing the herbal remedies at bay.

The sixteenth to eighteenth centuries were the era of European exploration of pharmacognosy. Johann Adam (1759–1809), a surgeon and ophthalmologist, published his 'Lehrbuch der Materia Medica' in 1811, which was a work on medicinal plants and their properties. At the end of the eighteenth century, crude drugs were still being used as powders, simple extracts, or tinctures. In 1803, a new era in the history of medicine began-the era of pure compound isolation, when morphine was isolated from opium. Subsequently other compounds such as strychnine (1817); quinine and caffeine (1820); nicotine (1828); atropine (1833); cocaine (1855) were isolated from different plant sources. During the nineteenth century, pharmacognosy was the most important pharmaceutical discipline and the chemical structures of many of the isolated compounds were determined. The first signs for a new era took new dimension with the introduction of a very successful synthetic drug aspirin using nature as lead for a new synthetic drug (Viktorin 1999). In the nineteenth century, microscopy was introduced in pharmacognosy for the quality control of crude drugs, and for many years, pharmacognosy remained confined with the microscope-based methods.

In the twentieth century, the discovery of important drugs from the animal kingdom and microorganisms, particularly hormones and vitamins, have become a very important source of drugs. In the 2nd half of the twentieth century, thin layer chromatography (TLC), gas chromatography (GC), high-pressure liquid chromatography (HPLC), spectrometric methods (MS, NMR) were introduced in pharmacognostical analysis and search for new biologically active compounds in plants. *In vitro* system bioassay was added at end of the twentieth century, and

during this period (1983–1994), a large number of antibiotic and antitumor principles from natural sources were discovered (Cragg et al. 1997).

(v) Modern era (from twentieth century onward)

Since inception in 1811, pharmacognosy has evolved considerably during the past two hundred years. In recent years, it has gained much importance because of the worldwide development of interest in natural products as lead molecules for new drugs as well as the increased use of complementary medicinal products in industrialized countries. At the beginning of the twenty-first century, emphasis has been put on (i) analysis, (ii) biological testing, and (iii) collaboration of pharmacognostical research. In pharmacognostical, high-throughput-based hyphenated computer-aided analytical techniques have been adopted to aid the traditionally used macroscopical, microscopical, and chemical methods of analysis parameters to optimize guarantees of quality, safety, and efficacy. The introduction of in vitro bioassays (back up by in vivo studies) has been the most important change in pharmacognostical research enabled bioassay-guided fractionation for the identification of the active compounds in plant or other extracts. In pharmacognostical research, the high-throughput-based bioprospecting program using robotic technology has been introduced to screen thousands of samples per day for new bioactive compounds in recent time.

Taxonomic identity of a species or taxon is fundamental to pharmacognostical research. Introduction of DNA barcoding as taxon identifier in pharmacognostical analysis in the twenty-first century is valuable, where DNA barcoding is an effective tool for identifying species, authenticating the herbals, and discriminating the adulterants of medicinal herbs. It may be helpful for identifying the closely related medicinal herbs used in substitution and adulteration purposes. The novel technique of identifying biological specimens using short DNA sequences from either nuclear or organelle genome is called DNA barcoding. As in plants no single-locus barcode exists, multilocus barcodes were suggested, and after evaluation of seven chloroplast genomic regions across the plant kingdom, the Consortium for the Barcode of Life Plant Working Group (CBOL) proposed a combination of *matK* and *rbcL* as plant barcodes. Because of its low discriminating ability in closely related species, the China Plant BOL Group proposed the addition of nuclear ITS (Internal Transcribed Spacer) to the *matK*+*rbcL* combination for enhancing the identification rates.

Pharmacognosy as an interdisciplinary subject admits collaborative research between scientists of different disciplines and pharmacognosist can be a valuable bridge between specialists and has much to offer to help pharmaceutical knowledge of phytomedicines to advance. Since nineteenth century, synthetic drugs have been replacing gradually plant-derived drugs (except antibiotics and antitumor drugs). Due to the development of experimentation with molecules and progress in biotechnology, biochemistry, molecular biology, and research on metabolism, new perspectives appear for natural products that renewed interest in natural resources leading to the high-level development of the subject. The multidisciplinary

characteristics of pharmacognosy are becoming more and more prominent as many new areas of research and study such as molecular pharmacognosy, neuropharmacognosy, industrial pharmacognosy are emerging in modern pharmacognosy with time.

In the modern era, the traditional herbalism has been officially regarded as a method of alternative medicine in many parts of the world, especially in some developed countries (e.g., USA, UK). The Traditional Chinese Medicine has been in use Chinese in hospitals. The World Health Organization estimated that 80% of people worldwide rely on herbal medicines for some part of their primary health care. In Germany, about 600–700 plant-based medicines are available and are prescribed by some 70% of German physicians. Many alternative physicians in the twenty-first century incorporate herbalism in modern medicine due to the diverse abilities plants have and their low number of side effects.

2.5 Drug Literature, Publication, and the Related Technical Words

2.5.1 Drug Literature and Publication

The knowledge developed on herbal medicine was transmitted at one time orally, and the earliest written form was the Egyptian papyri. This was followed gradually by clay tablets, parchments, manuscript herbals, printed herbals, pharmacopoeias and recently by computerized information database systems. The worldwide renaissance of herbal medicine in the recent years has created an urge for intensive studies in the field of pharmacognosy, and consequently, there appeared a large volume of literature and publications in different regions of the globe on all aspects of pharmacognosy. Drug literature and publication contain different information about drugs, their sources, therapeutic use, purity, adulteration, efficacy, etc., as well as many technical terms for convenience and brevity in describing the subject matters.

Depending on the originality and proximity to the origin, there may be three categories of information resources, e.g., primary, secondary, and tertiary. Primary sources are the original materials on which the research is based, e.g., scientific journals and articles reporting experimental research results, proceedings of meetings, conferences and symposia, technical reports, dissertations, patents, communications on e-mail and news groups. Once published, the primary source information serves as the basis for secondary sources. Review articles, literature review, textbook, Medline database search, works of criticism and interpretations, indexing and abstracting services, or otherwise ‘add value’ to the new information reported in the primary literature. Tertiary sources are a compilation of primary and secondary sources and tend to be factual in nature. The following list of works (textbooks and reference works) may provide some useful information about the gradual progress of the subject pharmacognosy.

a. Printed publication:

(i) Wallis TE. 1967. Text book of Pharmacognosy, 5th edn. London, Churchill Livingstone.
(ii) Wagner H and Horhammer L. (Ed.). 1971. Pharmacognosy and phytochemistry. Springer-Verlag, 175 Fifth AVe., New York, NY 10010.
(iii) Trease GE and Evans WC. 1972. Pharmaconosy, 10th edn. London, BillereTindall.
(iv) Ross MSF and Brain KR. 1977. An introduction to Phytopharmacy. Tunbridge Wells, Pitman Medical.
(v) Takatori J. 1980. Color Atlas of Medicinal Plants of Japan, 2nd edn. Tokyo, HirokawaPub. Company.
(vi) Mossa JS, Al-Yahya MA, And Al-Meshal IA. 1987. Medicinal Plants of Saudi Arabia. Riyadh, King Saud University.
(vii) Evans WC. 1989. Pharmaconosy, 13th edn. Second print 1994. London, BillereTindall.
(viii) Ali M. 1994. Text book of Pharmacognosy, CBS Publishers, Delhi, India.
(ix) Joshi SG. 2000. Medicinal Plants. Oxford & IBH Publishing Co. Pvt. Ltd., New Delhi, Calcutta.
(x) Lyle E. Craker and James E. Simon (Ed.). 2002. Herbs, Spices and Medicinal Plants, Recent Advances in Botany, Horticulture and Pharmacology, Vol. 1. Haworth Press, Inc., U.S.A., First Indian Reprent, 2002. CBS Publishers and Distributors, 4596/1A, 11 Darya Ganj, New Delhi, 110002 (India).
(xi) Ashutosh Kar. 2003. Pharmacognosy and Pharmacobiotechnology. New Age International (P) Ltd., Publishers, 4835/23 Ansari Road, Darya Ganj, New Delhi, 110002 (India).
(xii) Ghani M. 2003. Medicinal Plants of Bangladesh with Chemical Constituents and Uses, 3rd edn. Asiatic Society of Bangladesh, 5 Old Secretariat Road, Ramna, Dhkka 1000.
(xiii) Wagner H. 2004. Revival of pharmacognosy. Classical Botanical Pharmacognosy. Satellite Symposium: Annual Meeting of the American Society of Pharmacognosy, Phoenix, AZ.
(xiv) Ghani M. 2005. Textbook of Pharmacognosy. Institute of Medical Technology, House-68, Road-4, Block-B, Mirpur 12, Dhaka.
(xv) Khare CP (Ed.). 2007. Indian Medicinal Plants: An Illustrated Dictionary, Springer.
(xvi) Evans WC. 2005. Trease and Evans' Pharmacognosy, 15th Edition, Elsevier, Reed Elsevier India Pvt. Ltd., 17-A/1, Main Ring Road, Lajpat Nagar-IV, New Delhi-110 024, India.
(xvii) Evans WC. 2009. Trease and Evans' Pharmacognosy, 16th Edition, Elsevier.
(xviii) Roy Upton, Alison Graff, Georgina Jolliffe, Reinhard Länger, Elizabeth Williamson (Ed.) 2011. American Herbal Pharmacopoeia: Botanical

Pharmacognosy—Microscopic characterization of Botanical Medicines, CRC Press, Taylor & Francis Group. Boca Raton, London, New York.

(xix) Michael Heinrich, Joanne Barnes, Simon Gibbons, Elizabeth M. Williamson. 2012. Fundamentals of Pharmacognosy and Phytotherapy. 2nd Edn., Elsevier Publishing company.

(xx) Lu-qi Huang (Ed.). 2013. Molecular Pharmacognosy, Pub. Springer Netherlands.

(xxi) Abstracting Journals such as Chemical and Biological Abstracts, Journal of Biological Sciences, Journal of Pharmacognosy and Phytochemistry, Journals of Ethnobotany, Ethnopharmacology, Natural Products frequently contain research articles and review papers on medicinal plants, chemical constituents as well as therapeutic use of medicinal plants.

(xxii) The World Health Organization (WHO) encouraged the safe use of herbal medicine and published 117 herbal monographs in several volumes (I-IV+I). Other publications of WHO include the following:

(xxiii) WHO. 1998a. Quality Control Methods for Medicinal Plant Materials, World Health Organization, Geneva.

(xxiv) WHO. 1998b. Guidelines for the Appropriate Use of Herbal Medicines. WHO Regional Publications, Western Pacific Series. WHO Regional office for the Western Pacific, Manila. 3.

(xxv) WHO. 1998c. Basic Tests for Drugs, Pharmaceutical Substances, Medicinal Plant Materials and Dosage Forms. World Health Organization, Geneva.

(xxvi) WHO.2002. General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. World Health Organization, Geneva.

(xxvii) The National Medicinal Plants Board (NMPB) and Central Council for Research in Ayurvedic Science (CCRAS), under Department of AYUSH, Government of India developed a database (www.nmpb-mpdb.nic.in/). This will help the scientific community (students, teachers, practitioners) to keep themselves updated with the research and development work being carried out for a particular medicinal plant. Other databases are: Medicinal Plants Found in India, 7263 Medicinal plants of India Master list sourced from FRLHT, Bangalore—www.nmpb.nic.in/index1; Medicinal Plants of India; Ayurveda Encyclopedia of Indian Medicinal Plants/Herbs mainly using in Ayurveda-www.indianmedicinalplants.info/; Indian Medicinal Plants Database, www.medicinalplants.in/.

b. Online publications:

World Health Organization (WHO)

(i) WHO drug information-www.who.int/medicinedocs/index/assoc/s14162e/s14162e.pdf

(ii) WHO Regional Offices (African Region, Region of the Americas, South-East Asia Region, European Region, Eastern Mediterranean Region, Western Pacific Region): http://www.paho.org

(iii) American Herbal Pharmacopoeia (AHP) Sample Monograph: http://www.herbal-ahp.org/documents/sample/valerian.pdf
(iv) Med herb—http://www.medherb.com—Very comprehensive herbal information, folk lore, safety, and more.
(v) Herb world—Therapeutic herbal monographs written by David Hoffmann http://www.healthy.net/scr/MMList.aspx?MTId=1
(vi) European Medicines Agency (EMEA) Committee on Herbal Medicinal Products (HMPC) Community Herbal Monographs: http://www.emea.europa.eu/htms/human/hmpc/hmpcmonographs.htm
(vii) James Duke Data base-http://www.ars-grin.gov/duke/
(viii) Natural Health Products Directorate's (NHPD) Health Canada Compendium of Monographs: http://www.hc-sc.gc.ca/dhp-mps/prodnatur/applications/licen-prod/monograph/mono_list_e.html
(ix) World Health Organization (WHO) Monographs on Selected Medicinal Plants, Volume 1: http://whqlibdoc.who.int/publications/1999/9241545178.pdf
(x) World Health Organization (WHO) Monographs on Selected Medicinal Plants, Volume 2: http://whqlibdoc.who.int/publications/2002/9241545372.pdf.

2.5.2 Related Technical Words

Some of the technical words commonly used in drug literature and publication for convenience and brevity are described in the following paragraphs:

(i) **Drug and crude drugs**

The term drug includes any substance, natural or synthetic, having therapeutic properties and used in the diagnosis, treatment, cure or prevention of diseases of man and animals (without any addiction). Crude drugs are substances having therapeutic properties and pharmacological action, derived from natural sources such as plants, animals, or minerals and have undergone no further treatment to advance medicinal value except collection and drying for preservation, packing or marketing. Crude drugs include whole plant (tree, shrub, or herb), its morphological or anatomical parts, sap, extract, secretion, and other constituents; whole animal, its anatomical parts, extract, secretion, and other constituents. Inconsistency with dosing is a major drawback of crude drug. Triphala (three fruits), consisting of equal parts of three myrobalans taken without seed such as Amalaki (*Emblica officinalis*), Bohera (*Terminalia bellirica*) and Haritaki (*Terminalia chebula*), is an example of Ayurvedic crude drug.

(ii) Official, unofficial, and non-official drugs

Any drug included in the current issue of the pharmacopoeia of a country and officially used for therapeutic purposes is known as official drug. On the other hand, an unofficial drug is one which was previously included in pharmacopoeia, but not in current issue of the pharmacopoeia or any drug literature. Any substance possessing some medicinal properties and used for therapeutic purpose, but has never been included in pharmacopoeia or any drug literature of any country, is called non-official drug.

(iii) Herbal medicine, traditional medicine, natural substances, and formularies

The medicinal preparations that made from one or more plants, plant parts or organs and are used in the treatment, mitigation, management, etc., of various physical, mental ailments and injuries (both external and internal) on man or animal are considered as herbal medicine. They maybe in the form of powder, paste, infusion, decoction, distillate, or other naturally produced products of medicinal plants. In addition to active drug components, herbal medicine may contain inactive ingredient, which may serve the purpose of various pharmaceutical necessities (excipients) or may show synergistic and catalytic effects to enhance the therapeutic efficacy of the herbal medicine.

Medicines that are prepared by natural ingredients derived from plants, animals, and minerals or their mixture following the age-old method and wisdom are called traditional medicine. They may consist of whole or broken parts, powders, decoction, extract, or distillate of various medicinal plants, animals, and minerals or their combination in different proportion. The WHO defines traditional medicine as a system of medicine or treatment as the sum total of all knowledge and practices used in the diagnosis, prevention, and elimination of physical, mental, and social imbalance, relying exclusively on practical experience and observation transferred from generation to generation orally or in writing.

The products of natural origin, derived from plants, animals, and minerals or their products, which have not undergone any treatment to induce changes of natural molecular structure or configuration of any extent, are grouped as natural substances.

Formulary is a publication containing a list of patent medicines with their ingredients and brief notes on their pharmacological properties and therapeutic uses, published by the relevant authority of a country as a guide for the practitioners of medicine and pharmacy. Bangladesh National Formulary (BDNF), British National Formulary (BNF), American National Formulary (ANF), etc., are some the examples of national formularies. They publish their own formulary listing the medicines, which are manufactured, imported, sold, and used in the country.

(iv) Materia Medica, pharmacopoeia, and monographs

Materia Medica or materials of medicine include medicinal substances and products derived from natural sources. Pharmacopoeia is an official publication of a

country containing list of various drugs and therapeutic agents of current use with their monographs and specifies tests and standards for them. British pharmacopoeia (BP), Indian pharmacopoeia (IP), African pharmacopoeia (AP), International pharmacopoeia (IP), etc., are some examples. Pharmacopoeia includes monographs of various drugs and therapeutic agents, and description of a single item is regarded as monograph. In a monograph of a crude drug, an elaborate description is given on different heads such as official title, synonym, vernacular name, habit and distribution, collection, preparation, storage, identity test, test for adulteration, method of assay, chemical constituents, property and uses, doses, reaction, bibliography.

(v) **Cell constituents, primary and secondary metabolites**

Plant constituents are chemical substances present in the cells of plant or animal organs. These constituents may be active (active principle) when they exert physiological or pharmacological action on living organisms. Primary metabolites including carbohydrates, proteins, lipids, nucleic *acids,* etc*., are synthesized in plants through primary metabolic pathways* (e.g., *photosynthesis,* respiration, carbohydrate, protein, and nucleic acid synthetic pathways). The primary metabolites fulfill the basic needs of the life activities of plants and so they are present in all plants. Secondary metabolites such as alkaloids, terpenoids, phenolics are synthesized in plants (with the use of primary metabolites) through secondary metabolic pathways (e.g., shikimic acid pathway, mevalonic acid pathway). They are present in some selected taxonomic group of plants (not universally in all plants); apparently, they have no primary function and mostly serve the defensive (also attract pollinating agents) function in plants. Many of them are physiologically active and are used as therapeutic agents.

(vi) **Flora, indigenous, naturalized, exotic and endemic plants**

Plant population (or animal population) of a particular geographic area or a country represents flora (fauna) of the area or country. Bacteria and fungi living in the gut or on skin are often referred to as gut flora or skin flora, respectively. Flora, fauna, and other forms of life (e.g., fungi) of an area or country constitute biota of the area. Plants (or animals) growing (or living) in the region of their origin are indigenous to that area (geographic qualifier). Plants that were found in America before European settlement are indigenous to America. Plants (or animals) growing (or living) comfortably and completing their life cycle by their own naturally over time without any external aid in the foreign region or country (other than their native land) are called naturalized plants (or animals). Naturalized plants tend to become aliens if they are well adapted to their surroundings and spread uncontrollably pushing out indigenous plants by consuming precious resources. Plants (or animals) introduced intentionally or accidentally from outside to a new place or habitat where they were not found are exotic plants (or animals). For example, plants from Europe are exotic in North America or Japan and vice versa. They very often require a lot of resources to keep healthy growth. Endemic plants are indigenous, but they are naturally found in a relatively small region. They grow best

Photograph 2.11 Weights and scales, mortar and pestle, jars and surgical instruments—the tools of the apothecary's trade

under the prevailing conditions, provide food for all kinds of creatures, and help maintain genetic diversity

(vii) **Apothecary and apothecar**

A person who prepared and sold drugs for medicinal purposes in the past was apothecary (Photograph 2.11). Apothecary was derived from the Greek word apotheke (a repository or storehouse) via Latin apotheca to eventually old French apotecaire and entered English in the fourteenth century. In all, casesapothēca means storehouse but it became a title for the person who was skilled in preparing medicines. Apothecary is a historical name for a medical professional who formulates and dispenses material medica to physician, surgeon, and patients. These are now served by two groups of people, the pharmacists and the physicians. In some languages (e.g., German, Dutch, Scandinavian languages) and regions (e.g.,

Germany, Austria, Switzerland, Philadelphia, and Boston of USA) of the world, the term 'Apothecary' or 'Apotek' is still in use to designate a pharmacist or in the name of business. The term 'Apothecary' is mentioned even in some creative literature of William Shakespeare (e.g., Romeo and Juliet, King Lear), William Faulkner (A Rose for Emily), and J.K. Rowling (Harry Potter series).

2.5.3 Apothecary

Apothecary shops existed during the middle ages in Baghdad and were also active in Islamic Spain (Harley and Woodward 1992; Hadzović 1997; Al-Ghazal 2004). In Germany and German speaking countries like Austria and Switzerland, pharmacies or chemist stores are still called apothecaries or in German Apotheken. The Apotheke (store) is legally obligated to be run at all times by at least one Apotheker (male) or Apothekerin (female), who actually has an academic degree as a pharmacist. Bulk Apothecary now supplies drugs or medication as well as quality and affordable essential oils, soap making, and natural ingredients. The medieval apothecary was the ancestor of the modern general practitioner (GP). Apothecary is a more synonymous to the present-day pharmacist.

In early days, the apothecary himself used to collect, identify, and process the collected drug for compounding and dispensing them to the patient in addition to his job of diagnosing the disease and prescribing the remedy. From the fifteenth century to the sixteenth century, the apothecary gained the status of a skilled practitioner. But as the volume of knowledge of disease, therapeutic uses of medicinal plants, and technology of preparation of medicaments increased gradually over the years, it became impossible for a single person to manage these two different aspects of health management and specialization of the people involved in health management profession started developing on two different aspects. As a result, medicine and pharmacy started emerging along two separate paths: One group of people became specialized in diagnosing the ailment and prescribing the remedy for the patient (physicians), and another group of people became specialized in collecting, compounding, and dispensing the medicament (pharmacists). By the end of the nineteenth century, this bifurcation of the medical professions took their current institutional form, with defined role for physicians and surgeons, and the role of the apothecary was more narrowly conceived as that of pharmacist.

(viii) **Pharmacognosy and pharmacognosist**

Pharmacognosy is one of the important disciplines of increased significance in the curriculum of pharmacy. People working in the field of pharmacognosy are known as pharmacognosists (Photograph 2.12). Identification of the drug sources; (ii) determination of the morphological character; (iii) determination of chemical constituents, chemical nature, uses, potency, and purity of crude drugs; (iv) planning and designing of the cultivation of medicinal plants; and (v) prescription of the

Photograph 2.12 Pharmacognosists at work (Web source)

Photograph 2.13 Pharmacology research laboratory

detail processes of collection, drying, and preservation are the major functions of a pharmacognosist.

(ix) **Pharmacology and pharmacologist**

Pharmacology is a major subject in the curriculum of pharmacy. Pharmacology studies properties and interaction of drugs with living systems (Photograph 2.13). It includes everything related to drug, e.g., drug composition and properties, synthesis and drug design, molecular and cellular mechanisms, organ or systems' mechanisms, signal transduction or cellular communication, molecular diagnostics, interactions, toxicology, chemical biology, therapy, and medical applications and antipathogenic capabilities. Attention is also given to the effects of various doses of each medicinal substance and to the different ways in which medicine can be introduced into the body. The effects of poisons and the means to overcome them (i.e., toxicology) are studied in pharmacology. Pharmacodynamics and pharmacokinetics are two main areas of pharmacology. Pharmacodynamics studies the effects of the drug on biological systems, and pharmacokinetics studies the time

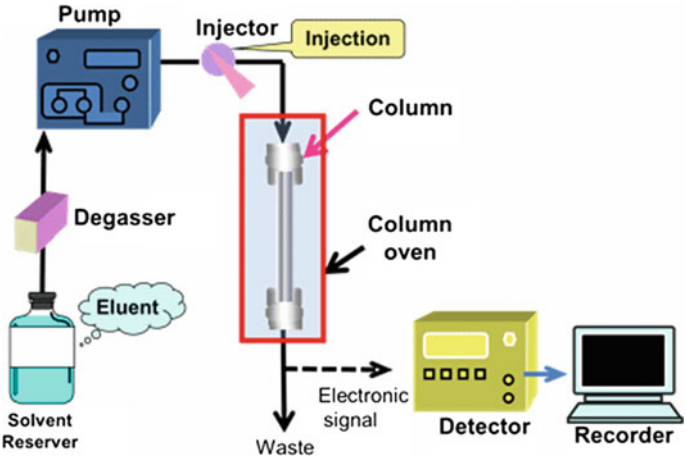
course of drug absorption, distribution, metabolism, and excretion from the biological systems. Pharmacology has adopted new technologies developed in other fields (e.g., bioinformatics, cheminformatics, computational chemistry, genetics, pharmacogenomics, proteomics) for drug discovery and drug design in the recent years. Pharmacology really makes sense of pharmaceutical studies.

Pharmacologists are biomedical scientists who research, develop, and test drugs and their effects on biological systems. Pharmacologists investigate the mechanisms underlying the effects of drugs and chemicals on living systems.

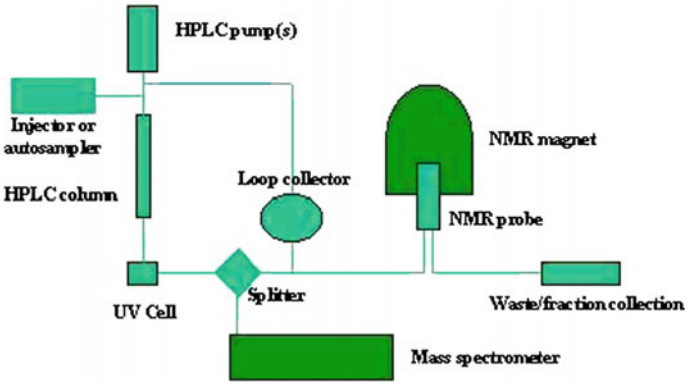
(x) **Pharmacy and pharmacist**

Pharmacy is a science and profession for safe and efficacious use of medication. It relates health science to chemical science. Subject pharmacy is divisible into several subdisciplines: (i) Pharmaceutics (convert medication and drugs to suitable drug dosage forms); (ii) pharmaceutical science (pharmaceutical chemistry, pharmacology, pharmacognosy, phytochemistry, etc.); (iii) pharmacy practice (dispensing medication and optimization of patients' care); and (iv) pharmaceutical analysis (analysis of pharmaceutical drug and its stability using various analytical techniques like GC-NMR, HPLC, etc.) are the main lines of pharmacy (Photographs 2.14, 2.15, 2.16, 2.17).

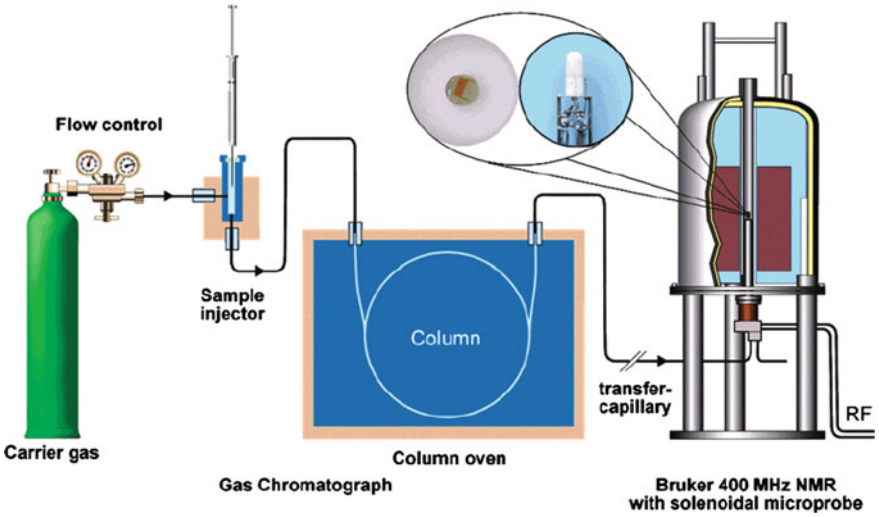
Pharmacy practice has been divided into hospital pharmacy and clinical pharmacy since the late twentieth century. Pharmacy curriculum at graduate and postgraduate levels emphasizes six basic courses including (i) pharmaceutical chemistry (application of chemical sciences to pharmacy);(ii) pharmacology (action of drugs in the body); (iii) pharmacognosy (sources of natural drugs obtained from plants or animals, either directly or indirectly); (iv) pharmacy administration (business management); (v) pharmacy practice; and (vi) the clinical component of the



Photograph 2.14 Components of HPLC (consisting of consisting of pump, injector, column, detector, recorder, degasser, column heater, or oven)



Photograph 2.15 Typical layout of a HPLC-NMR system (a hyphenated system)



Photograph 2.16 Hyphenation of gas chromatography to Microcoil 1 H Nuclear Magnetic Resonance Spectroscopy

pharmacy. In addition to these courses, four basic sciences such as mathematics, physics, chemistry, and biology are included in pharmacy curriculum.

2.5.4 Pharmacists

Pharmacists (chemists or druggists) are healthcare professionals who practice in pharmacy. Pharmacists undergo university-level education to understand the

Photograph 2.17 Pharmaceutical research and testing laboratories

biochemical mechanisms and actions of drugs, drug uses, therapeutic roles, side effects, drug interactions, etc. Pharmacists are educated in pharmacology, pharmacognosy, pharmaceutical chemistry, pharmacy practice, pharmaceutics, pharmacy law, physiology, anatomy, pharmacokinetics, pharmacodynamics, drug delivery, pharmaceutical care, and compounding of medications along with mathematics, physics, chemistry, and biology. Additional curriculum may cover diagnosis with emphasis on laboratory tests, disease state management, therapeutics, and prescription medications. Pharmacists dispense prescription medications to patients and offer expertise in the safe use of prescriptions. Pharmacists interpret and communicate their specialized knowledge to patients, physicians, and other healthcare providers. The most common pharmacist positions are that of a community pharmacist (a retail pharmacist, first-line pharmacist, or dispensing chemist), or a hospital pharmacist, where they instruct and counsel on the proper use and adverse effects of medically prescribed drugs and medicines. Pharmacists may also practice in a variety of other settings, including industry, wholesaling, research, academia, military, and government.

Pharmacology is not synonymous with pharmacy, although the two terms are frequently confused. Pharmacology is a scientific field of study, and a pharmacologist studies the effects of drugs on the body of living organisms to produce a change in function, while pharmacy is a professional field and area of study, and a pharmacist (community or hospital pharmacist) studies weights and measures, solubilities, incompatibilities, qualities, drug reactions, the extraction of active principles, and the making of preparations suitable for the use in the practice of medicine. Pharmacology is a more specific science that may be studied either independently or as a part of pharmacy curriculum, and pharmacy also involves the study of sciences (e.g., pharmacology, pharmaceutics, pharmacokinetics) and also more profession-based elements (e.g., counseling patients, checking and filling prescriptions, the manufacturing process of drugs) (Photograph 2.18).

Photograph 2.18 Compounding and dispensing pharmacy

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Chapter 3
Medicinal, Non-medicinal, Biopesticides, Color- and Dye-Yielding Plants; Secondary Metabolites and Drug Principles; Significance of Medicinal Plants; Use of Medicinal Plants in the Systems of Traditional and Complementary and Alternative Medicines (CAMs)

Abstract Medicinal plants are used in the treatment of different ailments. They cannot be distinguished from other plants by morphological characteristics except their pharmacological effects and contain therapeutic agents. Non-medicinal plants are morphologically similar to medicinal plants except some of the members produce active compounds that function either as poisons, pesticides, hallucinogens or teratogens. Poisonous plants produce poison, and pesticide plants are useful in pest management. Poisons and pesticides cause injury, illness, or death to a person if he tastes, smells, and gets it on skin or in eye by their local or systematic action or both. However, the boundary line between medicinal and non-medicinal poisonous, pesticide, hallucinogen plants, etc., is not sharply demarcated, e.g., *Azadirachta indica*, *Malus* sp., *Prunus* spp., *Manihot esculenta*, *Abrus precatorius*, *Brugmansia* sp., *Cicuta douglasii*, *Colchicum autumnale*, *Datura* spp., *Digitalis purpurea*, *Nepenthes attenboroughii*, *Nerium oleander*, *Ricinus communis*, *Strophanthus gratus*, *Strychnos nux-vomica* contain different bioactive compounds including azadirachtin, nimbin, amygdalin, linamarin, and lotaustralin (cyanogenic glycoside), abrin, ricin (ribosome-inactivating protein), aconitine (alkaloid), scopolamine, hyoscyamine, atropine (tropane alkaloids), solanine (glycoalkaloid), nerioside, oleandroside, ouabain (cardiac glycoside); saponins, strychnine (extremely bitter deadly alkaloid), etc. which may be used either as drug principles or poisons or toxins depending on dose and intention of use. Plant-derived pesticides like pyrethrin, rotenone, nicotine, strychnine, and scilliroside from *Chrysanthemum cinerariifolium*, *Pachyrhizus erosus*, *Nicotina tabacum*, *S. nux-vomica*, *Drimia maritime*, respectively, are widely used. Hallucinogens are psychoactive agents of natural origin and cause distortions in perceptions of reality (hallucinations) by disrupting the interaction of nerve cells and the neurotransmitter serotonin. Hallucinogens are mostly alkaloids, and mescaline, psilocin, psilocybin, ibogaine,

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LSD, etc. are some of the examples of common hallucinogen drugs. Topically active hallucinogens include solanaceous belladonna, henbane, mandrake, datura. Pollen from hundreds of weed, grass, and tree plant species, e.g., ragweed, maple, oak, Acacia, Bermuda grass, castor bean, red clover can trigger allergic reactions (allerginosis) in many people every year. Teratogens affect the development of an embryo, pregnancy or may cause a birth defect in the child. Diverse group of compounds, e.g., vitamin D, quinine, anagyrine, and other alkaloids aspirin, marijuana, cannabinols, etc., have shown teratogenicity compounds are synthesized by different plant of the genera including *Lupinus*, *Veratrum*, *Conium*, *Astragalus*, *Nicotiana*, *Trachymene*, *Datura*, *Prunus*, *Sorghum*, *Senecio.* Some of these plants also cause congenital defects. Natural color and dyes are obtained from plants, animals, or minerals without chemical processing. Roots, berries, bark, leaves, and wood of plants, as well as fungi and lichens, are the major natural sources. Many of the natural dyes like turmeric, annatto, and saffron are food additives and some have pharmacological effects and possible health benefits. The pharmacological effects of medicinal plants are mainly due to their secondary metabolites (e.g., alkaloids, terpenoids, phenolics, glycosides, antibiotics.) produced in the secondary metabolic pathways, which are often species specific, i.e., found in only a small set of species in a narrow phylogenetic group while the primary metabolic pathways and primary metabolites (e.g., carbohydrates, proteins, lipids, nucleic acids, and others) are ubiquitous in plant species. Innumerable numbers of medicinal herbs or their active therapeutic secondary metabolites are used in both traditional and modern systems of medicines. The secondary metabolites may be grouped as nitrogenous (e.g., alkaloids, non-protein amino acids, amines, cyanogenic glycosides, glucosinolates.) and non-nitrogenous (e.g., terpenoids, steroids, saponins, phenolics, flavonoids, polyacetylenes, polyketides, phenylpropanoids.) metabolites. Therapeutically important alkaloids include morphine and codeine from the opium poppy, cocaine from the coca plant, atropine from the deadly nightshade Belladonna, vincristine and vinblastine from the periwinkle, quinine from the bark of the cinchona, caffeine from coffee, tea, and cola plants, nicotine is present in tobacco. Monoterpenes are exemplified by the aromatic oils (e.g., menthol) contained in the leaves of some members of mint family, and pyrethroids are present in the flowers of Chrysanthemum; diterpenes paclitaxel (taxol) is found in bark of the Pacific yew tree; triterpenoids (plant steroids) phytoecdysones are a group of plant sterols are obtained from Tinospora, Asparagus; tetraterpenoids include important pigments (e.g., beta-carotene, lycopene) and are available in colored plant parts. Salicylic acid, a simple phenolic compound, can be obtained from the bark of white willow (*Salix alba*); isoflavones, lignin (complex phenolic macromolecule), anthocyanins, and anthocyanidins (phenolic pigments) impart pink and purple colors to flowers and fruits. Medicinal herbs include entire plant, plant parts, e.g., leaves, flowers, fruits, seeds, stems, wood, bark, roots, rhizomes, or other plant parts in entire, fragmented form as well as fresh juices, gums, fixed oils, essential oils, resins, etc. Herbal finished products include comminuted or powdered herbal materials, or extracts, tinctures, and fatty oils, and mixed herbal product. Finished and mixed

herbal products may contain excipients in addition to the active ingredients. Herbal principles that have made valuable contribution to the development of modern medicine include ephedrine, digitoxin, salicin, reserpine, atropine, colchicine, quinine, codeine, vincristine, ipecac, physostigmine, sena, cocaine, capsaicin, scopolamine. Allamandin, helenalin, indicine-*N*-oxide, mezerien and laphacol, insulin effectors, boswellic acid, withanolides, ruscogenin, harpagoside, etc. are some therapeutically promising molecules identified recently from herbs. *Artemisia annua* provides new generation anti-malaria drug; bark of *Prunus africana* is useful for prostate cancer; *Sutherlandia* is important for its value to HIV/AIDS sufferers. Recent discovery like β-adrenergic and paclitaxel from *Lingusticum wallichii* and *Taxus brevifolia*, respectively, signify the role of plant as an inexhaustible treasure of modern medicines. Different traditional systems of medicine including the (i) Traditional Chinese, (ii) Ayurvedic, (iii) Unani, (iv) Homeopathy, (v) Siddah, (vi) Native North American Herbal, (vii) Western Herbal, (viii) Yoga, (ix) Naturopathy, (x) Folk medicine have been using hundreds of medicinal plants and other accessories in diagnosis, treatment, prevention, and elimination of physical, mental, or social imbalance since antiquity. Complementary and alternative medicine (CAM) is a non-mainstream medicine consisting of a wide range of healthcare practices, products, and therapies, e.g., homeopathy, naturopathy, chiropractic, magnetic field therapy, energy medicine, various forms of acupuncture, Traditional Chinese medicine, Ayurvedic medicine, Christian faith healing. Modern medicine is based on evidence and clinical proof and is practiced by medical graduates or postgraduates educated in medical college, institute, or university after completion of the prescribed medical curriculum in a stipulated period of time. Before the twentieth century, most medicines were extracted from plants (herbal medicines), and since the twentieth century, thousands of modern drugs have been synthesized from an organic compound. The active principles of herbal medicine are comparable with the contents of modern medicine, and many common drugs in use today were derived from herbal sources (e.g., aspirin from willow bark, digitalis from foxglove) and therefore, herbal medicine may not be considered as mere quackery. There are numerous advantages of herbal medicine including its effectiveness for long-standing health complaints irresponsive to traditional medicine, fewer side effects, safer to use over time, well tolerated by the patient(e.g., prescription drug vioxx-rofecoxib for arthritis was recalled due to increased risk of cardiovascular complications), inexpensive compared to modern drugs, and easy availability of herbs. However, herbal medicine and herbalist may not be proved effective for sudden, serious illnesses, serious trauma, appendicitis, or a heart attack as a conventional doctor using modern diagnostic tests, surgery, and drugs. Self-dosing with herbs, overdosing, misidentification of herbs from the wild source, interaction with prescription drugs, lack of quality assurance, etc. are some of the important disadvantages of herbal medicine.

Keywords Medicinal plants · Drug principles · Biopesticides · Traditional systems · Modern medicine

3.1 Medicinal Plants and Their Characteristics, Secondary Metabolites, and Drug Principles

Medicinal plants contain inherent active ingredients and are used for different therapeutic purposes. According to the World Health Organization (WHO 1977), a medicinal plant is any plant, which in one or more of its organ contains substances that can be used for the therapeutic purposes or which are precursors for the synthesis of useful drugs. *Aloe barbadensis, Andrographis paniculata, Catharanthus roseus,* and *Rauvolfia serpentine,* etc. are few examples of common medicinal plants. This definition includes those plants whose therapeutic properties and constituents have been established scientifically and also plants that are regarded as medicinal but which have not yet been subjected to thorough investigation. After further elaboration, the WHO (2001) includes herbal preparations produced by different physical or biological processes such as extraction, fractionation, purification, concentration within the definition of medicinal plant.

Medicinal plants provide people with medicines to prevent disease, maintain health, or cure ailments. Medicinal plant possesses health-promoting characteristics, gives temporary relief of symptomatic problems or has curative properties. In one form or another, they benefit virtually everyone on Earth. Besides the therapeutic importance, they are also important for nutrition, toiletry, bodily care, incense, and ritual healing. Roots, leaves, seeds, bark, or all parts of a medicinal plant possess therapeutic, tonic, purgative, or other pharmacologically active principle or precursor for synthesis of useful drugs. Aromatic plants are important medicinally for their aroma and flavor.

Medicinal plants cannot be distinguished from other plants by morphological characteristics except chemical constituents by virtue of which they exert beneficial pharmacological effects on the animal body. It has now been established that medicinal plants synthesize and accumulate one or more secondary metabolites like alkaloids, terpenoids, phenolic compounds and contain minerals and vitamins. Secondary metabolites are the active drug principles of herbal medicine. They are synthesized in plants following different metabolic pathways.

3.1.1 Metabolites and Metabolic Pathways: Primary and Secondary Metabolites of Plants and Related Pathways

Metabolites are compounds synthesized by plants for both essential (primary metabolites) and specific (secondary metabolites) functions through different metabolic pathways (Fig. 3.1). Plants have tremendous biosynthetic potentialities, and they synthesize thousands of diverse primary and secondary metabolites. Primary metabolites (carbohydrates, proteins, lipids, nucleic acids, and others) are essential for growth and development and so they are ubiquitous in plant kingdom while

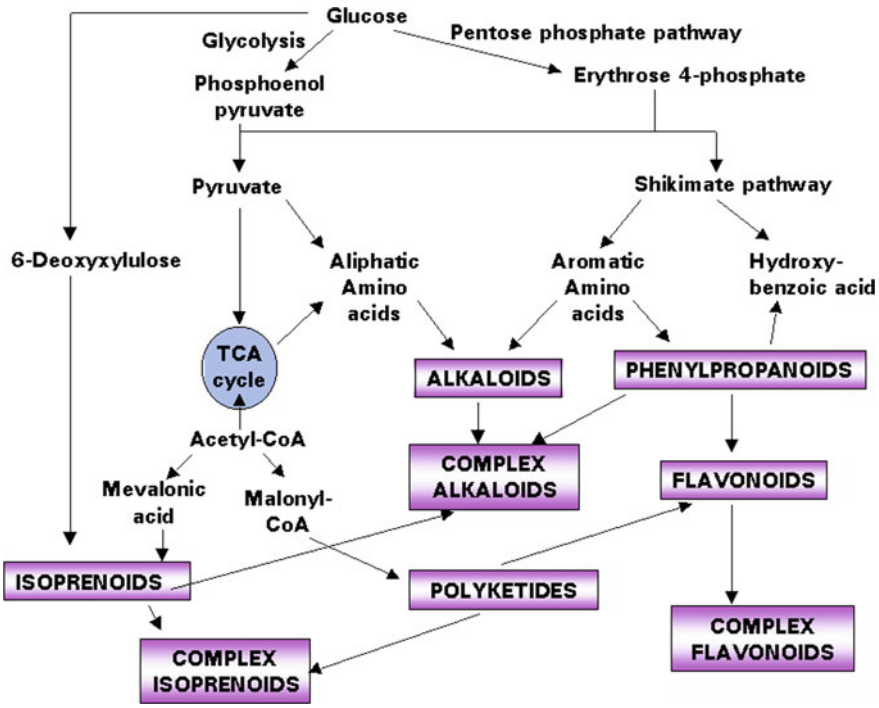


Fig. 3.1 Secondary metabolites (*colored back ground*) are derived from primary metabolites (*white back ground*)

secondary metabolites (alkaloids, phenolics, sterols, steroids, essential oils, glycosides, lignins, terpenoids, and others) are the metabolic end products and perform some specific functions such as pollinator attraction or defense against herbivory, and secondary metabolites are variously distributed in the plant kingdom. Most primary metabolites are identical among most organisms, whereas secondary metabolites are numerous, wide spread and are accumulated by plant cells in very small quantities than primary metabolites. Primary metabolites are the products of fundamental metabolic pathways such as glycolysis, the Krebs cycle, and the Calvin cycle while secondary metabolites are the products of mevalonic acid, shikimic acid, etc. pathways. Examples of primary metabolites include energy-rich fuel molecules (sucrose, starch, and lipids), structural components (cellulose, proteins, and lipoproteins), high molecular building blocks (amino acids and carboxylic acids), enzymes (proteins), informational molecules (DNA and RNA), and pigments (chlorophyll). Some primary metabolites are precursors for the synthesis of secondary metabolites (amino acids for alkaloid synthesis), and for that secondary metabolites are considered as the end products of primary metabolites. Primary metabolites are produced during the growth phase (trophophase) of cell while secondary metabolites are produced during the non-growth phase (idiophase) of the cell.

So far, >0.1 million secondary metabolites of plant origin have been reported (Terryn et al. 2006) and structures close to 50,000 have already been elucidated (De Luca and St Pierre 2000). The secondary metabolites or natural products can be classified into several groups according to their chemical classes, such alkaloids, terpenoids, and phenolics (Harborne 1984). The recorded use of plants in the treatment of various ailments dates back to antiquity (Sofowora 1993; Cragg et al. 1999). Therapeutic properties of medicinal plants are due to their secondary metabolites and these metabolites can be used as a drug, drug precursors, drug prototypes, and pharmacological probes. Some others may have accessory pharmaceutical and culinary importance.

Many of these natural products have been shown to present interesting biological and pharmacological activities and are used as chemotherapeutic agents or serve as the starting point in the development of modern medicines (Verpoorte 1998, 2000). These metabolites or natural products are synthesized in plants from the primary metabolites, and in addition to therapeutic properties, they serve some other purposes including growth regulation, allelopathic interactions, and defense against predators and infections and for attracting pollinators. Secondary metabolic compounds are often involved in key interactions between plants and their abiotic and biotic environments (Facchini et al. 2000). Biosynthesis of primary metabolites is ubiquitous in plant species while that of secondary metabolites is restricted to selected plant groups.

a. Synthesis of primary metabolites—they are initially synthesized from simple ingredients like CO_2 and H_2O using solar energy in green leaf through photosynthetic process. Calvin-Basham (C3), Hatch-Slack (C4), Glycolytic, TCA cycle, etc. are the major primary metabolic pathways.
b. Synthesis of secondary metabolites—the carbon skeleton produced in photosynthetic process is utilized for the production of secondary metabolites through various secondary processes. Shikimic acid, malonic acid, mevalonic acid, MEP pathways, etc. are some important secondary metabolic pathways.

These are shown in Fig. 3.1.

$CO_2 + H_2O$

↓↑←Photosynthesis

Primary carbon metabolism

↓↑

Three major groups of secondary products are:

1. Alkaloids (12,000 alkaloids), heterocyclic compounds made from amino acids;
2. Terpenoids (29,000), polymer of 5C isoprene unit made from acetyl-CoA, and
3. Phenolic compounds (8000), made from PEP, erythrose 4C sugar through shikimate pathway or malonate/acetate pathway.

The above groupings may be rearranged in the following way:

1. Nitrogenous secondary metabolites: (a) Alkaloids (12,000), (b) Non-protein amino acids (6000), (c) Amines (100), (d) Cyanogenic glycosides (100), (e) Glucosinolates (100);
2. Non-nitrogenous secondary metabolites: (f) Terpenoids (29,000): monoterpene-1000, sesquiterpene-300, diterpenes-1000, triterpenes, steroids, saponins-4000; (g) Phenolics (8000); (h) Flavonoids 2000; (i) Polyacetylenes-1000; (j) Polyketides-750; (k) Phenylpropanoids-500.

3.1.2 Alkaloids

Alkaloids are a large group of nitrogen-containing compounds, which are known to occur in approximately 20% of all flowering plants. Closely related plant species often contain alkaloids of related chemical structure. The primary metabolites from which they are derived include amino acids such as tryptophan, tyrosine, and lysine. Alkaloids accumulate in plant organs such as root, leaves, barks, fruits, seeds, and other organs of plant. Alkaloids with important medicinal uses include morphine and codeine from the opium poppy, cocaine from the coca plant. These alkaloids act on the nervous system and are used as painkillers. Atropine from the deadly nightshade plant also acts on the nervous system and is used in anesthesia and ophthalmology. Vincristine and vinblastine from the periwinkle plant are inhibitors of cell division and are used to treat cancers of the blood and lymphatic systems. Quinine from the bark of the cinchona tree is toxic to the *Plasmodium* parasite and has long been used in tropical and subtropical regions of the world as an anti-malarial drug. Caffeine from coffee, tea, and cola plants are used as stimulant. Nicotine is present in tobacco. Nicotine preparations are used as an aid in smoking cessation and insecticide.

3.1.3 Terpenoids

Terpenoids are classified by the number of five-carbon isoprenoid units they contain. Monoterpenes (containing two C5-units) are exemplified by the aromatic oils (such as menthol) contained in the leaves of members of the mint family; pyrethroids are monoterpene esters and are present in the flowers of chrysanthemum and related species, used commercially as insecticides. Diterpenes are formed from four C5-units. Paclitaxel (Taxol) is a diterpene, found in bark of the Pacific yew tree, a potent inhibitor of cell division in animals; paclitaxel is a powerful chemotherapeutic agent against ovarian cancer. Triterpenoids (formed from six C_5^- units) comprise the plant steroids, some of which act as plant hormones; phytoecdysones

are a group of plant sterols that can protect plants from insect attack. Tetraterpenoids (eight C_5^- units) include important pigments such as beta-carotene, which is a precursor of vitamin A, and lycopene, which gives tomatoes their red color. Rather than functioning in plant defense, the colored pigments that accumulate in ripening fruits can serve as attractants to animals, which actually aid the plant in seed dispersal. Rubber is a polyterpene.

3.1.4 Phenolic Compounds

Phenolic compounds contain one or more aromatic rings bearing a hydroxyl functional group. Salicylic acid is simple phenolic compound that can be important in defense against fungal pathogens. Aspirin is a derivative of salicylic acid, used as a drug to reduce inflammation, pain, and fever in humans. Isoflavones have strong antimicrobial activity. Lignin is a complex phenolic macromolecule and is the main component of wood. Anthocyanins and anthocyanidins are phenolic pigments that impart pink and purple colors to flowers and fruits and function as attractants of insects and other animals and accomplish pollination and fruit dispersal.

Medicinal herbs perform several functions such as (i) source of bioactive compounds for direct use in modern medicine (e.g., digoxin, digitoxin, morphine, reserpine, taxol, vinblastine, vincristine); (ii) lead compounds for synthesis of modern drugs of higher activity and/or lower toxicity (e.g., synthesis of metformin, nabilone, oxycodone, taxotere, teniposide were based on herbal lead compounds like galegine, morphine, taxol, podophyllotoxin, khellin, respectively); (iii) agents for pharmacologic tools (e.g., lysergic acid diethylamide, mescaline, yohimbine); and (iv) herbal remedy (e.g., cranberry, echinacea, feverfew, garlic, ginkgo, St. John's wort).

3.1.5 Secondary Metabolites and Drug Principles

About 12,000 bioactive compounds have been isolated from medicinal plants but the number is considered to be a fraction (<10%) of the total (Lai and Roy 2004; Tapsell et al. 2006). Alkaloids contributed the largest number of drugs such as anticholinergics (atropine), analgesics (opium), anti-parasitics (quinine), anti-cholinesterases (galantamine), antineoplastics (vinblastine and vincristine), followed by terpenoids, which made an equally important contribution to human health (e.g., Na^+/K^+ pump-inhibiting cardiac glycosides from *Digitalis* spp., anti-neoplastic paclitaxel, anti-malarial artemisinin, anti-inflammatory triptolide, and many other). The presence of these secondary metabolites in medicinal plants probably explains their various uses in traditional medicine. Examples of some other bioactive compounds from plant sources include apigenin from parsley;

crocetin from saffron; curcumin from turmeric; diallyl sulfide from garlic; epigallocatechin gallate (polyphenols) from green tea; fisetin from strawberries and apples; genistein from soybean; gingerol from gingers; isothiocyanates, diindolylmethane (DIM)/Indole-3-carbinol (I3C), kaempferol from tea, broccoli, grapefruit; lycopene from tomato; phenethyl isothiocyanate (PEITC) from Brassica vegetables; cyanidins, resveratrol from grapes; rosmarinic acid from rosemary; resveratrol from grapes; sulforaphane from broccoli; and silymarin from milk thistle. Some of the commonly used drug principles of secondary metabolic origin are aconitine from *Aconitum* spp., non-toxic atisine from *Aconitum heterophyllum*, lobeline from *Lobelia* inflata, nicotine from *Nicotiana tabacum*, strychnine from *S. nux-vomica*, digoxin from *Digitalis purpurea*, atropine from *Atropa belladonna*, morphine from *Papaver somniferum*, etc. In modern medicine, use of about 122 compounds of plant origin has been identified and 80% of them show similarity in their use in both the traditional and modern medicines (Fabricant and Farnsworth 2001).

The use of natural phytochemicals has been an emerging strategy to prevent, impede, delay, or cure many diseases including cancer, aids, diabetes, arthritis, cardiovascular, migraine, dementia (neurodegenerative diseases), (Wang et al. 2012). Recently, researchers have identified some new therapeutically important molecules from different herbs, e.g., (i) allamandin from *Allamanda cathartica*, elephantpoin from *Elephantopus elatus,* helenalin from *Helenium autumnale*, indicine-*N*-oxide from *Heliotropium indicum*, mezerien from *Daphne mezereum,* and laphacol from *Stereospermum suaveolans* against cancer; (ii) insulin effectors from *Ajuga reptens*, galagine from *Galega officinalis*, pinitol from *Bougainvillea spectabilis*, chirantin from *Momordica charantia*, gymnemic acid from *Gymnema sylvestre* against non-insulin dependent diabetes, alkaloid tecomonine from *Tecomastans* are considered to be active principle to fight diabetes; (iii) guggulsterones from *Commiphora mukul*, boswellic acid from *Boswellia serrata*, withanolides from *Withania somnifera*, ruscogenin from *Ruscus aculeatus*, harpagoside from *Harpago phytumprocumbens* are endowed with anti-arthritic and anti-rheumatoid activities; (iv) parthenolides-sesquiterpenes lactones from *Chrysanthemum parthenium* has shown promising results against the century old disease migraine; (v) plaunotol from *Croton sublyratus* has potent and wide spectrum anti-peptic ulcer action; (vi) sarmentosin from *Sedum sarmentosum*, waweizichun and schisantherin from *Schisandra chinensis* are potential to lower raised liver enzymes in viral hepatitis. (vii) michellamine-b from *Ancistrocladus korupensis*, calanolide-a from *Calophyllum lanigerum*, costatolide-a from *Caulophyllum teymani*, prostratin from *Homalanthus nutans*, concurvone from *Conospermum* sp., etc. would be the suitable cure for Aids; (viii) bacosides A and B from *Bacopa monnieri*, forskolin from *Coleus forskohlii*, proanthocyanidins from grape seed, polyphenols from *Camellia sinensis*, huperzine from *Huperzia serrata*, pycnogenol from *Pinus maritime*, γ-linoleic acid from *Borago officinalis,* and vinpocetine from *Vinca minor* are potential antioxidants; and (ix) hypericin from *Hypericum* is responsible for antidepressant activity.

3.1.6 Significance of Medicinal Plants to Man

Man in his struggle for existence has always turned to nature and relied on plants for the fulfillment of his physical, emotional, and spiritual needs. Plants form an integral part of any society at any time. The herbal medicines of ancient times practiced by the Assyrians (4000 BC), Sumerians (3500 BC), Indians (3500 BC), Chinese (3000 BC), Egyptians (2500 BC), and others. Medicinal plants have been identified and used throughout human history. Various systems of medicine including Ayurveda, Siddha, Unani, Homeopathy, Naturopathy, and Allopathy use innumerable number of plant species for curing human ailments and diseases. Medicinal plants are source of a large number of drug principles and lead compounds. At least 12,000 such compounds have been isolated so far; a number estimated to be less than 10% of the total (Lai and Roy 2004; Tapsell et al. 2006). Chemical compounds in plants mediate their effects on the human body through processes identical to those already well understood for the chemical compounds in conventional drugs; thus herbal medicines do not differ greatly from conventional drugs in terms of how they work. This enables herbal medicines to be as effective as conventional medicines, and therefore they are significant to human being.

Medicinal plants are significant to human being because (i) many of the modern medicines are produced indirectly from medicinal plants, e.g., aspirin; (ii) plants are directly used as medicines by a majority of cultures around the world, e.g., Chinese medicine and Indian medicine; (iii) many food crops have medicinal effects, e.g., garlic; (iv) medicinal plants are resources of new drugs, and it is estimated there are more than 250,000 flower plant species and they are assumed to be the source of many new drugs; (v) studying medicinal plants helps to understand plant toxicity and protect human and animals from natural poisons; and (vi) cultivation and preservation of medicinal plants protect biological diversity, e.g., metabolic engineering of plants.

The results of the present day scientific research in herbals have clearly demonstrated the importance of medicinal herbs for new bioactive principles even in this synthetic era as many pathogenic microbes are developing resistance against the synthetic medicines. Medicinal herbs may be an inexhaustible source of active drug principles for many diseases as they are capable of producing thousands of diverse bioactive secondary metabolites more efficiently than a modern biosynthetic laboratory. A total of about 35,000–70,000 plant species are used for medicinal purposes across the world. The medicinal plants along with pharmaceutical industry, also find application in cosmetic, agricultural, and food industries. Only a minor fraction of the world plant flora ($\sim$20%) has so far been studied for bioactive principles but in spite of that a significant proportion of modern medicines ($\sim$60%) are related to medicinal herbs for their origin in one way or another. Ancient herbal knowledge coupled with scientific principles may come to the forefront to provide powerful remedies to eradicate the diseases.

3.2 Factors Affecting the Production of Secondary Metabolites in Medicinal Plants

Plant secondary metabolites are unique sources for pharmaceuticals, food additives, flavors, and industrially important biochemicals. They are synthesized by different biochemical pathways and their synthesis, qualitative as well as quantitative contents in plants are affected by abiotic (environmental, nutritional) and biotic (pathogens, predators, wounds) factors or stresses. Plants under stress produce various regulating elicitors or signal molecules. Transmission of signals in plants occurs by 'semiochemicals,' comprised of terpenes, phenylpropanoids, benzenoids and other volatile compounds (Tuteja and Sopory 2008). Such signal molecules create variation in the accumulation as well as biogenesis of secondary metabolite profiles. Secondary metabolites synthesized under stress play a major role in the adaptation of plants to the environment and in overcoming stress conditions (Seigler 1998). Secondary metabolites also contribute to the specific odors, tastes, and colors in plants (Bennett and Wallsgrove 1994). Different abiotic factors such as temperature, humidity, light, moisture or water content, drought, mineral nutrients, salinity, toxic elements, and CO_2 influence the growth of a plant and secondary metabolite production. Biotechnology of in vitro cell (tissue and organ) culture is an effective way for both studying and producing plant secondary metabolites without the interference of environmental factors. It also provides means for plant improvement by genetic manipulation for high metabolite yield. The production of secondary metabolic compounds is low (>1% dry weight) and depends greatly on the physiological and developmental stage of the plant (Rao and Ravishankar 2002). Some of the plant-derived secondary metabolites include drugs like morphine, codeine, cocaine, quinine, vinca alkaloids, belladonna alkaloids, colchicines, physostigmine, pilocarpine, reserpine, and steroids like diosgenin, digoxin and digitoxin, flavonoids, phenolics. Synthesis of many of these compounds is influenced by environmental factors, e.g., stimulation of polyphenol synthesis and accumulation response to biotic or abiotic stresses, formation of phenyl amides, and dramatic accumulation of polyamines in bean and tobacco under the influence of abiotic stresses (Edreva et al. 2000), stimulation of anthocyanin accumulation by various environmental stresses, such as UV, blue light, high-intensity light, wounding, pathogen attack, drought, sugar, and nutrient deficiency (Winkel-Shirley 2001), nitrogen and phosphate deficiencies directly influenced the accumulation of phenylpropanoids (Dixon and Paiva 1995), potassium, sulfur, and magnesium deficiency increased phenolic concentrations, low iron level can cause increased release of phenolic acids from roots (Chalker-Scott and Fnchigami 1989), anthocyanins were increased in response to salt stress (Parida and Das 2005), but salt stress decreased anthocyanin level in the salt-sensitive species (Daneshmand et al. 2010), accumulation of anthocyanins under drought stress and at cold temperatures, Cu^{2+} and Cd^{2+} induced higher yields of secondary metabolites such as shikonin (Mizukami et al. 1977) and also on the production of digitalin, low

soil temperatures caused an increase in levels of steroidal furostanol and spirostanol saponins, environmental abiotic factors influenced saponins contents in the roots, leaves, stems, bulbs, flowers, and fruit of *Panax ginseng* (Szakiel et al. 2010) temperature and light quality influenced the production of ginsenoside in hairy root culture of *P. ginseng* (Yu et al. 2005), American ginseng plants exposed to longer sunlight had higher root ginsenoside contents than those exposed to shorter periods of direct sunlight (Li et al. 1996).

3.3 Contribution of Medicinal Plants to the Development of Modern Medicine

The importance of the medicinal plants for curing disease has been documented in history of all civilizations. Medicinal plants constitute an important natural wealth of a country and may be used in pharmaceutical, cosmetic, agricultural, and food industry. They play a significant role in providing primary healthcare services to rural people, serve as therapeutic agents as well as important raw materials for the manufacture of traditional and modern medicine. The use of traditional medicines and medicinal plants in most developing countries as therapeutic agents for the maintenance of good health has been widely observed (UNESCO 1996). Modern pharmacopoeia still contains at least 25% drugs derived from plants and many others, which are synthetic analogues, built on lead (prototype) compounds isolated from plants. Interest in medicinal plants as a re-emerging health aid has been fueled by the rising costs of prescription drugs in the maintenance of personal health and well-being and the bioprospecting of new plant-derived drugs (Lucy and Edgar 1999). The growing recognition of medicinal plants and herbal remedies is due to several reasons, e.g., escalating faith in herbal medicine and increasing reliance on the use of medicinal plant resources in the industrialized societies for extraction and development of drugs and chemotherapeutics (UNESCO 1998). According to the WHO, medicinal plants would be the best source to obtain a variety of drugs. Therefore, such plants should be investigated to better understand their properties, safety, and efficacy (Nascimento et al. 2000).

Medicinal plants produce bioactive compounds used mainly for medicinal purposes. These compounds either act on different systems of animals including man and/or act through interfering in the metabolism of microbes infecting them. The microbes may be pathogenic or symbiotic. In either way, the bioactive compounds from medicinal plants play a determining role in regulating host-microbe interaction in favor of the host. So the identification of bioactive compound in plants, their isolation, purification, and characterization of active ingredients in crude extracts by various analytical methods is important. The instant rising demand of plant-based drugs is unfortunately creating heavy pressure on some selected high-value medicinal plant populations in the wild due to over-harvesting. Several of these medicinal plant species have slow growth rates, low population

densities, and narrow geographic ranges (Nautiya et al. 2002), therefore they are more prone to extinction (Jablonski 2004).

Medicinal plants constitute an ever important source of many new drugs. In recent years, for example, the Chinese plant *A. annua*, has become the essential in a new generation of anti-malaria drugs. The plant is now being grown in East African countries to supply pharmaceutical manufacturers in Europe. The bark of the tree *Prunus africana* is used in making treatments for prostate cancer. *Sutherlandia*, a native plant of South Africa, is being increasingly recognized for its value to HIV/AIDS sufferers. Other African plants, such as Devil's Claw and African Geranium, are also gaining popularity as herbal medicines, particularly in Europe. Substantial amount of foreign exchange can be earned by exporting medicinal plants to other countries. In this way, indigenous medicinal plants play significant role of an economy of a country.

Drugs of natural origin continue to be important for the treatment of many diseases worldwide. The relevance of this discipline in terms of research and teaching has increased in the last few decades as people in developed countries have turned to the use of herbal remedies for the self-medication of minor diseases. However, many phytomedicines require further investigation for their clinical effectiveness, while others need to be thoroughly investigated for their potential health risks or interactions with prescription drugs. Pharmacognosy has played a diverse role in the discovery, characterization, production, standardization, quality control, and other aspects of herbal drugs.

Pharmacognosy contributed enormously to the development of modern medicine. Herbal drug principles that have made valuable contributions to modern drug preparation at commercial scale include ephedrine, digitoxin, salicin (source of aspirin), reserpine, atropine colchicine, quinine, codeine, vincristine, ipecac, physostigmine, sena, cocaine, capsaicin, scopolamine. from *Ephidra sinica*, *Digitalis purpurea, Salix alva, Rauvolfia serpentina, Atropa belladonna, Colchicum autumnale, Cinchona officinalis, P. somniferum, C. roseus, Cephaelis ipecacuanha, Physostigma venenosum, Cassia acutifolia, Erythroxylum coca, Capsicum frutescens, Datura metal,* respectively. Recent discovery like β-adrenergic—a cardiovascular drug and paclitaxel—an antineoplastic (anticancer) drug from *Lingusticum wallichii* and *Taxus brevifolia*, respectively, signifies the role of plant as an inexhaustible treasure of modern medicines. It is estimated that about 40% of all medicines is either natural products or their semi-synthetic derivatives (Jacob 2009). About 30% of all modern drugs are derived from plants and in the USA, and in many European countries, thousands of herbal and related products are available in the market. Most early medicines like aspirin, digitoxin, morphine, quinine, and pilocarpine were derived from plant sources, and the natural product compounds are still a significant source of new drugs, especially in the anticancer, antihypertensive, anti-infective, immuno-suppression, and neurological diseases (Butler 2004).

3.4 (i) Non-medicinal, (ii) Poisonous, (iii) Psychoactive (Stimulant, Hallucinogenic, Depressant, and Aphrodisiac), (iv) Allergenic, (v) Teratogenic and (vi) Toxic Plants

(i) Non-medicinal plants do not exert a therapeutic effect or plants which are not medically prescribed are described as non-medicinal plants. Non-medicinal plant substances include laxative, cellulose, and pectin fiber. Despite the medically justified uses in China, Germany, Japan, and the USA, ephedrine and pseudoephedrine, extracted from the plant or synthesized, are official in most countries, many consumers in the USA use products containing Ephedra for non-medicinal purposes such as weight loss, athletic performance enhancement, energy boost.

(ii) A plant or its product that causes injury, illness, or death of man, domestic or wild animal is called poisonous plant. A poison is a substance that causes harm to organisms when sufficient quantities of it are absorbed, contacted with skin or eye, smoked, inhaled or ingested. A poison may make an organism sick, impair biological functions or other minor harms, and even cause death. Poisons may synthetic chemicals (dioxins, sarin, pesticides, nerve gases, etc.) or natural (belladonna, botulinum, muscarine, tetrodotoxin, lead, arsenic, etc.). Botulinum is deadly neurotoxin produced by the bacterium *Clostridium botulinum* (Münchau and Bhatia 2000; Nigam and Nigam 2010). Belladonna contains deadly poisonous tropane alkaloids (atropine, scopolamine, hyoscyamine, etc.). Muscarine is an alkaloid poison produced by the mushroom *Amanita muscaria*. Tetrodotoxin synthesized by the Japanese globefish (*Spheroides rubripes*) is extremely toxic even if ingested in tiny amounts. Saxitoxin is accumulated in shellfish (but synthesized by marine phytoplankton dinoflagellates) and causes paralytic shellfish poisoning of man, a deadly syndrome, on consumption. The fruits and seeds of *Menispermum canadense* and *Datura stramonium* are poisonous when swallowed. Corn cockle (*Agrostemma githago*) contains a cyanophore type of glycoside, and its seeds cause death when they are present in excessive quantities in wheat flour.

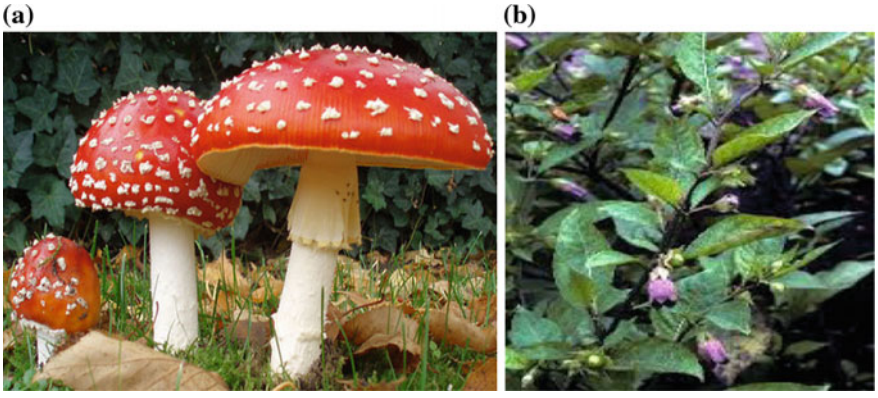
The words poisons and toxins are often used interchangeably. Toxins and toxicants are narrower definitions for the word poison. The term toxin refers to a poison produced by a living organism, such as a microorganism, a plant, or an animal. In everyday practice, the terms poison and toxin are often used interchangeably. A toxin is a specific type of poison, i.e., poisonous substances are produced within living cells or organisms such as a microorganism, a plant, or an animal. Such poisons of biological origin are often designated as biotoxins or 'natural toxins.' The fields of veterinary medicine and zoology often distinguish a poison from a toxin and from venom. Venoms are poisons or toxins that are injected by a bite (from snake or spider) or sting (from bee or wasp) to cause their

effect in human or other animals. Therefore, a toxin is a poison produced by a living organism, and venom is a toxin injected from a living organism into another. It may be concluded that venom is a toxin and a toxin is a poison, not all poisons are toxins, not all toxins are venoms. Toxins are poisons produced by organisms in nature, and venoms are toxins injected by a bite or sting (this is exclusive to animals).

The term 'poison' is often used colloquially to describe any harmful substance, particularly corrosive substances, carcinogens, mutagens, teratogens, and harmful pollutants, and to exaggerate the dangers of chemicals. Paracelsus (1493–1541), herald of modern toxicology, opined that everything was poison and there was poison in everything depending only on the dose used. Substances not legally required to carry the label poison can also cause a medical condition of poisoning when used in excess. Water is essential and safe for animal but in taking in excess may cause death and then becomes poison. Some poisons are also toxins. Poisons are produced by animals, vegetables, or bacterium, e.g., tetanus and botulism are caused by the bacterial proteins: tetanus neurotoxin-TeNT and botulinum neurotoxins-BoNT (serotypes AG or antigen), respectively. A distinction between the two terms is not always observed, even among scientists. The derivative forms 'toxic' and 'poisonous' are synonymous.

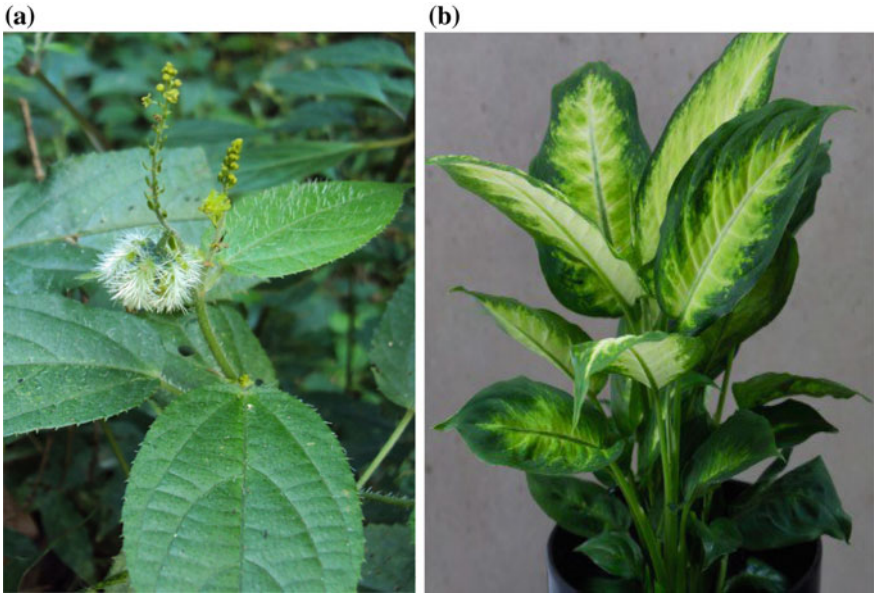
A product that may be safe in a normal dose may be unsafe at overdose levels. Poison hemlock, oleander, the seed of rosary pea, elderberry, and castor bean are so poisonous that small amounts may be fatal if eaten. Poison can also be a good thing used in a wrong way, like vitamins, medicines, etc. Toxicology is the science of poisons, and it includes the study of harmful effects of chemicals on living organisms.

Toxic plants produce toxins or substances that can cause disturbances to organisms (Photograph 3.1a, b). A toxin is a poisonous substance produced within



Photograph 3.1 **a** *Amanita muscaria* (fly agaric or magic mushrooms) produces toxin muscarine (*Source* http://sciencelearn.org.nz. Copyright: Onderwijsgek Creative Commons Attribution ShareAlike 3.0). **b** *Atropa belladonna* (*Source* http://plants.usda.gov/core/profile?symbol=ATBE)

living cells or organisms. Toxins can be small molecules, peptides, or proteins that are capable of causing disease on contact with or absorption by body tissues interacting with biological macromolecules such as enzymes or cellular receptors. Toxins vary greatly in their toxicity, ranging from usually minor (e.g., *T. involucrata* leaf sting or bee sting) to almost immediately deadly (such as botulinum toxin). Based on effects or functions, toxin may be hemotoxin that causes destruction of red blood cells (hemolysis), phototoxin that causes dangerous photosensitivity, cytotoxins are toxic at the level of individual cells, necrotoxins cause necrosis (i.e., death) in the cells they encounter and destroy all types of tissue, neurotoxins primarily affect the nervous systems of animals, myotoxins are small, basic peptides found in snake and lizard venoms and cause muscle tissue damage, etc. Exotoxins are excreted by an organism and endotoxins and are released after disintegration. mycotoxins, microbial biotoxins, phytotoxins, and animal biotoxins are grouped together as biotoxins or toxins of biological origin. Ricin from castor beans, T-2 mycotoxin from certain toxic mushrooms, etc. are examples of plant toxins. Major toxic plants may cause serious illness or death if ingested, minor toxic plants may cause minor illnesses such as vomiting or diarrhea if ingested. The juice or sap of these plants (minor toxic) contains oxalate crystals which can irritate the skin, mouth, tongue, and throat, resulting in throat swelling, breathing difficulties, burning pain, and stomach upset. Some toxic plants may cause dermatitis. The juice, sap, or thorns of such plants may cause a skin rash or irritation. Toxic plants, especially the house plants, can be a hazard to children and pets, as well as to



Photograph 3.2 **a** *Tragia involucrata* (Indian stinging nettle, Bichuti); **b** *Dieffenbachia* sp. (dumb cane plant)

elderly persons with dementia. Philodendron, pothos, Dieffenbachia, arrowhead, lily, ivy, oleander, caladium, mother-in-law's tongue, Indian stinging nettle, etc. are some of the examples of common toxic plants (Photograph 3.2a, b).

(iii) Psychoactive plants are very common in nature. These plants produce a large number of secondary metabolites that may affect the brains and mental states and are capable of inducing altered states of consciousness of the humans who ingest them. They are many naturally grown as well as cultivated psychoactive plants. Some of them are opium poppy, Salvia, Cannabis, ayahuasca, betel nut, tobacco, jimson weed, and coca. Different psychoactive plants contain different metabolites as active principles such as morphine, codeine, thebaine, narcotoline, and noscapine; alkaloids in opium poppy (*P. somniferum*), arecoline alkaloid (a potent muscarinic cholinomimetics) and polyphenols in betel nut (*Areca catechu*), alkaloid *cocaine* (methylbenzoylecgonine) in coca (*Erythroxylum coca*), ergoline alkaloids in heavenly blue' morning-glory (Ipomoea tricolor), ibotenic acid in fly agaric mushrooms (*A. muscaria*), atropine, hyoscyamine and scopolamineas in jimson weed (*D. stramonium*), thujone in wormwood (*Artemisia absinthium*), kavalactones in kava (*Piper methysticum*), diterpenoid 'Salvinorin A' in Salvia (*Salvia divinorum*), psilocybin and psilocin in magic mushrooms (*Psilocybin* sp.), phenethylamine alkaloids, principally mescaline in peyote (*Lophophora williamsii*), carboline harmala alkaloids (harmine, harmaline, and harmalol) function as MAOIs (monoamine oxidase inhibitors) and found in the seeds of *Peganum harmala* and leaf of tobacco, and DMT (dimethyltryptamine) in ayahuasca (*Banisteriopsis caapi*), delta-9-THC (delta-9-tetrahydrocannabinol) in Indian hemp (*Cannabis sativa*), alkaloid nicotine in tobacco (*N. tabacum*), etc. are found to work as active constituents. It appears that almost all chemicals that have psychoactive properties are alkaloids except the active compound of marijuana, delta-9-tetrahydrocannabinol (delta-9-THC). Caffeine, nicotine, cocaine, morphine, ephedrine, etc. are common psychoactive alkaloids.

Plant-derived psychoactive principles influence the central nervous system and mental states of human being in many different ways by influencing the release of neurotransmitters (chemical messengers within the nervous system) such as acetylcholine, serotonin, dopamine, norepinephrine, or mimicking their actions, and at least four classes of psychoactivities are reported, e.g., stimulant, hallucinogenic, depressant, and aphrodisiac. Psychoactive compounds are found primarily in angiosperms and fungi. Angiosperm families especially known for having plants with psychoactive properties include: Cactaceae (*L. williamsii*), Cannabaceae (*C. sativa*), Solanaceae (*A. belladonna*, *Datura* spp., *Mandragora officinarum*, *Nicotiana* spp.), Malphiginaceae (*Banisteriopsis* sp.), Rubiaceae (coffee), Papaveraceae (*P. somniferum*), Piperaceae (*P. methysticum*), Erythroxylaceae (*E. coca*), Convolvulaceae (morning-glory). Psilocybin mushrooms or psychedelic mushrooms are sources of psilocybin and psilocin (indolealkylamines).

Psychoactive compounds were unknown in the animal kingdom, but now it is found in toads (buffotoxins: 5-MeO-DMT and bufotenin both are hallucinogenic tryptamines). Psychoactive compounds are known to occur in all parts of the plant, from the roots, leaves, bark, stem, and seeds.

Stimulation of mental state is characterized by excitement and enhancement of mental alertness and physical activity, reduce fatigue, improve concentration, and suppression of hunger due to intake of cocaine, caffeine, ephedrine, etc., the well-known plant-derived stimulants.

A plant that produces hallucinogenic effects (hallucinations) due to its hallucinogenic principles is called hallucinogenic plant. Such plant exerts substantial influence on perception of space, time, emotions, etc. when illusions appear real to its consumer. Hallucination is a visual terminology, and it happens when users see images, hear sounds, and feel sensations that seem very real but do not exist (i.e., distortions in perception, thought, and mood that depart from reality) and often induces a dream like mental state. Hallucinogens cause their effects by disrupting the interaction of nerve cells and the neurotransmitter serotonin. Mescaline, psilocybin, ibogaine, LSD (lysergic acid diethylamide), peyote, marijuana, etc. are some of the examples of common hallucinogen drugs. A hallucinogen is a psychoactive agent (mostly alkaloidal in nature) and causes hallucinations, perception anomalies, and other substantial subjective changes in thoughts, emotion, and consciousness. *Hallucinogenic plants* have been used by man for thousands of years, probably since he began gathering plants for food. The above ground part of the cactus peyote (*L. williamsii,*), nutmeg or mace (*Myristica fragrans*), bark of the woody vine ayahuasca (*B. caapi*), seeds of morning glories (*Ipomoea violacea*, *Rivea corymbosa*), wormwood (*Artemisia absinthium*), diviner's sage (*S. divinorum*) leaf, and deadly nightshade (*A. belladonna*) are few examples of hallucinogenic plants. Some of the poisonous fungi when taken orally produce hallucinations. The examples are *Amonito*, *Psilocyb*e, and *Conocybe*. Certain cacti contain protoalkaloids, some of which have marked hallucinogenic properties.

Depressants induce dull mental awareness, reduce physical performance, and induce sleep or trance-like state. Opium and its derivatives, morphine, and heroin are classic examples of depressants. Narcotic substances including opiates, alcoholic beverages, and kava also induces central nervous system depression, resulting in numbness, lethargy, and sleep. Narcotic substances are dangerously addictive. So nicotine and the stimulant cocaine are also narcotic substances.

The term 'Aphrodisiac' was derived from Aphrodite, the Greek goddess of sex, love, and beauty. An aphrodisiac is defined as an agent (food or drug) that arouses sexual desire and increases libido (sex drive) when consumed. Aphrodisiacs are distinct from substances that address fertility issues such as impotence or secondary sexual dysfunction such as erectile dysfunction (ED). All parts of the datura *plant*, fresh or dried, are used worldwide as *aphrodisiacs.* Medicinal plants with aphrodisiac potential include *Abelmoschus manihot* (Malvaceae), *Anacyclus pyrethrum* (Asteraceae), *Asparagus racemosus* (Liliaceae), *Butea frondosa* (Papillionaceae), *Chenopodium album* (Chenopodiaceae), *Crossandra infundibuliformis* (Acanthaceae), *Curculigo orchioides* (Amaryllidaceae), *Dactylorhiza hatagirea*

(Orchidaceae), *Glycyrrhiza glabra* (Papillionaceae), *Mimusa pudica* (Mimosae), *Syzygium aromaticum* (Myrtaceae), *Tinospora cordifolia* (Menispermaceae), *Cinnamomum camphora* (Lauraceae), *Hibiscus sabdariffa* (Malvaceae), *Allium sativum* (Alliaceae), (Singh et al. 2013). Saffron, nutmeg, clove, passionflower, maca root, etc. are the herbs that enhance female libido. Maca (*Lepidium meyenii*), also called the Peruvian viagra (sildenafil), contains macamides or maca alkaloids as active ingredient while acai (*Euterpe oleracea*) contains lot of zinc as active aphrodisiac and antioxidant agent.

(iv) Allergenic plants produce substances that function like allergen. A large number of plants give rise to allergic reactions in certain individuals; produce an antigen–antibody reaction which results in the liberation of histamine or identical compounds causing allergic symptoms. Allergies are commonly asthma and dermatitis. An allergen is a type of antigen that produces an abnormally vigorous immune response by stimulating a type-I hypersensitivity reaction in atopic individuals (a syndrome characterized by a tendency to be hyperallergic) through Immunoglobulin E (IgE) responses. Such antigen-immune system reactions are called allergies. Most humans mount significant IgE responses only as a defense against parasitic infections but atopic individuals may respond to many non-parasitic environmental antigens and stimulate inappropriate IgE production, leading to type-I hypersensitivity. Allergens can be found in a variety of sources, such as dust, mite excretion, pollen, pet dander, or even royal jelly. Food allergies differ from food sensitivity, but some foods such as peanuts, nuts, seafood, shellfish, pumpkin, brinjal cause of serious allergies in many people. Food allergies differ from food sensitivity and foods including peanuts nuts, seafood shellfish, etc. cause serious allergy in many people. Many trees (acacia, alder), flowers (dandelion, sunflower), grasses (Bermuda grass, Johnson grass), weeds (baccharis, cocklebur, rag weed), and cultivated plants (castor bean, red clover) can trigger allergic reactions: Hundreds of plant species including acacia, alder, ash, beech, birch, cedar, cottonwood, date palm, elm, mulberry, juniper, oak, phoenix palm, willow release their pollen into the air every year causing allergic reactions in many people.

Pollens of grasses like timothy (*Phleum pratense*), cocks foot (*Dactylis glomerata*) and perennial rye (*Lolium perenne*) as well as that of nettle (*Urtica dioica*), plantain (*Plantogo* spp.) and ragweeds (*Ambrosia* spp.) are responsible for seasonal hay fever. A number of common molds produce spores which cause rhinitis and asthma in sensitive individuals. *Rhus* spp. like *R. radicans* (poison ivy), *R. toxicodendron* (poison oak), *R. deversiloba* (Pacific poison oak), and *R. vemix* (poison elder) (fam. Anacardiaceae) contain allergens which produce severe dermatitis associated with watery blisters. Sesquiterpene lactones from the species of Asteraceae, Lauraceae, and Magnoliaceae and from the Liverwort *Fruifoma* (Fam. Jubulaceae) are a major class of compounds causing allergic contact dermatitis in human.

(v) Plants that cause congenital defects are teratogenic plants. Teratogens affect the development of an embryo or fetus, may halt the pregnancy or may cause birth defect. It is a significant problem in livestock as well as in humans; causes are environmental rather than hereditary. Many diverse group of compounds (e.g. vitamin D, quinine, anagyrine and other alkaloids, aspirin, marijuana cannabinols) have shown some evidence of teratogenicity in laboratory rodents and some these compounds are synthesized by different plant of the genera *Leucaena*, *Lupinus, Veratrum, Conium* (1st group) *Astragalus, Nicotiana*, *Trachymene* (2nd group) *Datura, Prunus, Sorghum, Oxytropis, Veratrum, Vicia, Senecio* (3rd group), etc. On the basis of available information, the first category represents known teratogenic plants with known teratogens, the second category represents known teratogenic plants with unidentified teratogens, and the third category represents mostly the suspected teratogenic plants (Keeler 1984).

3.5 Biopesticides

A pesticide is a chemical used to prevent, destroy, or repel pests and pesticides of biological or natural origin (i.e., derived from plants, animals, microbes, and certain minerals) are biopesticides. For example, pyrethrum, rotenone (isoflavone), neem oil (azadirachtin), sesame oil, clove oil, rosemary oil, canola oil, various essential oils including citrus and eucalyptus oil, onion, garlic, tea as well as copper and baking soda have pesticidal effects and are considered biopesticides. Pesticides are one group of substances whose toxicity is their prime purpose. A conventional or synthetic pesticide is usually toxic substance and directly kills or inactivates animal or plant pests (including insects, termites, nematodes, molluscs, rodents, weeds, fungi, and microorganisms) that cause economic damage to crop, ornamental plants, and domestic by interrupting the normal metabolic processes in the pest organisms. Biopesticides include substances that interfere with mating such as insect sex hormones (pheromones) and various other scented plant extracts that attract insect pests to traps. Pesticides often are classified according to the type of organism they are intended to control, viz. insecticides, molluscicides, nematocides, rodenticides, fungicides, herbicides, and fumigants. Biopesticides are less toxic, target specific, and effective at low concentration. Now, plant-incorporated-protectants (PIPs) are pesticidal substances that plants produce from genetic material that has been added to the plant, e.g., gene for the Bacillus thuringiensis or Bt pesticidal protein has been introduced into the plant's own genetic material.

3.5.1 Weedicides

Any undesirable plant is known as weed, e.g., a weed may be a dandelion in a lawn, a thistle plant in a vegetable garden, or mustard in a clove field. Undesirable plants

in gardens interfere in the growth of cultivated plants by consuming most of the available water contents and minerals of the soil. If weeds are allowed to grow, they will soon acquire the possession of the garden and gradually destroy the more delicate, cultivated plants. Similarly, the quality of the field crops, especially grains, becomes poor due to the presence of weed seeds. Weeds exert allelopathic interference on crops with the chemicals they secrete and, in addition, many of the weeds contain toxins, allergens, etc. (Qasem and Foy 2001; Singh et al. 2003).

3.6 Natural Colors and Dyes

Natural colorants or dyes are dyes derived from plants, invertebrates, or minerals. The majority of natural dyes are vegetable dyes from plant sources—roots, berries, bark, leaves, and wood—and other organic sources such as fungi and lichens. In the early twenty-first century, the market for natural dyes in the fashion industry is experiencing resurgence. Western consumers have become more concerned about the health and environmental impact of synthetic dyes in manufacturing, and there is a growing demand for products that use natural dyes. The European Union, for example, has encouraged Indonesian batik cloth producers to switch to natural dyes to improve their export market in Europe.

Some of the plant sources of color or dye such as alder bark (*Alnus rubra*) yields orange; barberry (*Mahonia* sp.) yields yellow orange (with alum) very strong and permanent color and any part of the plant will work; bloodroot (*Sanguinaria canadensis*) root when cut open produces a good orange to reddish orange color; butternut tree (*Juglans cinerea*) bark, seed husks, etc., produce light yellow-orange color; carrot (*Daucus carota*) roots produces orange color; *Eucalyptus* spp. all parts, leaves, and bark produce beautiful shades of tan, deep rust red, yellow, green, orange, and chocolate brown color; giant coreopsis (*Coreopsis gigantea*) yields bright permanent orange with alum; lichen (*Orchella weed*) (*Roccellaceae*) produces gold, purple, red etc. color; lilac (*Syringa vulgaris*) twigs produce yellow/orange shade; onion (*Allium cepa*) skin produces orange color; pomegranate peel with alum produces color anywhere from orange to khaki green; Sassafras leaf; turmeric (*Curcuma longa*) rhizome dyed cloth turns orange or red if it is dipped in lye. Some other dye-yielding plants are Catechu or Cutch tree (brown), Gamboge tree resin (dark mustard yellow), Himalayan rubhada root (yellow), Indigofera plant (blue), Kamala tree (red), Larkspur plant (yellow), Madder root (red, pink, orange), Myrabolan fruit (yellow, green, black), etc. Some animal sources of dye are as follows: Cochineal insect (red), Cow urine (Indian yellow), Lac insect (red, violet), Murex snail (purple), Octopus/Cuttlefish (sepia brown).

3.7 Importance of Drugs from Natural Sources

Natural products and their derivatives have been recognized for many years as a source of therapeutic agents and of structural diversity. Nature has been a source of medicinal products for millennia, with many useful drugs developed from plant sources and important drugs from natural sources that revolutionized treatment of serious diseases.

The World Health Organization estimated in 1985 that approximately 65% of the population of the world predominately relied on plant-derived traditional medicines for their primary health care, while plant products also play an important, though more indirect role in the healthcare systems of the remaining population who mainly reside in developed countries (Farnsworth et al. 1985). A survey of plant-derived pure compounds used as drugs in countries hosting WHO-Traditional Medicine Centers indicated that, of 122 compounds identified, 80% were used for the same or related ethnomedical purposes and were derived from only 94 plant species (Farnsworth et al. 1985). Drugs based on traditional medicine leads like. khellin, sodium chromoglycate, galegine, metformin, papaverine, verapamil are known and some relevant examples are khellin, from *Ammi visnaga*, which led to the development of chromolyn (in the form of sodium chromoglycate) as a bronchodilator; galegine, from *Galega officinalis*, which was the model for the synthesis of metformin and other bisguanidine-type antidiabetic drugs; and papaverine from *P. somniferum* which formed the basis for verapamil used in the treatment of hypertension (Fabricant and Farnsworth 2001). The latter plant is better known as being the source of painkillers such as morphine and codeine (Buss and Waigh 1995) and the best example of ethnomedicine's role in guiding drug discovery and development is that of the anti-malarial drugs, particularly quinine and artemisinin. *A. annua* (Quinhaosu) was long used in TCM (Wongsrichanalai et al. 2002). Artemisinin analogues are now used for the treatment of malaria in many countries (O'Neill and Posner 2004).

3.8 Use of Medicinal Plants in Indigenous Traditional Systems of Medicine: Ayurveda, Unani, Homeopathy, Aromapathy, Siddha, Yoga, Naturopathy, Folk Medicine, Native North American Medicine, Western Herbal Medicine

Traditional system of medicine is an art of healing based on traditional use of plants, animals, and other natural substances, and cultural habits, social practices, religious beliefs, and in many cases, superstitions of the present and previous generations of people. The World Health Organization (WHO 2003) defines traditional medicine as the sum total of all knowledge and practice (whether explicable

or not) used in the diagnosis, prevention, and elimination of physical, mental, or social imbalance based exclusively on practical experience and observations handed down from generation to generation, verbally or in writing.

There are at least five principal and some other minor traditional methods through which herbal medicines are prescribed:

(i) Traditional Chinese Medicine (TCM); (ii) Traditional Ayurvedic Medicine; (iii) Traditional Unani Medicine; (iv) Homeopathy; (v) Siddah; (vi) Native North American Herbal medicine; (vii) Traditional Western Herbal; (viii) Yoga; (ix) Naturopathy and (x) Folk medicine.

In Bangladesh and in other countries of the Indian subcontinent, the traditional healthcare systems practiced include Ayurvedic, Unani, Homeopathic, and Folk medicine systems.

3.8.1 Traditional Chinese Medicine (TCM)

The Traditional Chinese Medicine (TCM) was originated in the remote past. Archeological evidence of medicinal herbs and acupuncture needles dates back to about 5000 BC and the earliest known herbal formularies date back to the Qin and Han Dynasties (221 BC–206 BC). TCM diagnosis looks for patterns of disharmony or imbalances rather than treating specific diseases. TCM treatments for restoring balance and harmony usually involve the prescribing of herbal tea, decoctions, acupuncture, specific diet counseling, massage, and other therapies including cupping, moxibustion, exercise, and meditation. TCM herbal formulas are organized according to a complex hierarchy including chief, deputy, assistant, and envoy herbs. Chief-herbs directed against the main pattern of disharmony; deputy: herbs with two functions: (i) aid the chief herb(s) in treating the principle pattern, and (ii) serve as a main herb directed against a coexisting pattern; assistant-herbs with three functions: (i) reinforce the effect of the chief and deputy herbs, and (ii) mitigate side effects of the chief or deputy herbs, or (iii) have an effect that is opposite to that of the chief herb; envoy herbs with two functions—(i) focus the actions of the formula on a certain channel or area of the body, and (ii) harmonize and integrate the actions of the other herbs.

3.8.2 Traditional Ayurvedic Medicine

Ayurvedic or Ayurveda is one of the oldest systems of holistic medicine in the world. Ayurveda was originated in India and recorded more than 5000 years ago in Sanskrit, in the four sacred texts called the Vedas: the Rig Veda (3000–2500 BC), Yajur Veda, Sam Veda, and Atharva Veda (1200–1000 BC). The term Ayurveda means 'Science of life,' a medical science wherein health is achieved through a blending of physical, mental, social, moral, and spiritual welfare. Its adherents

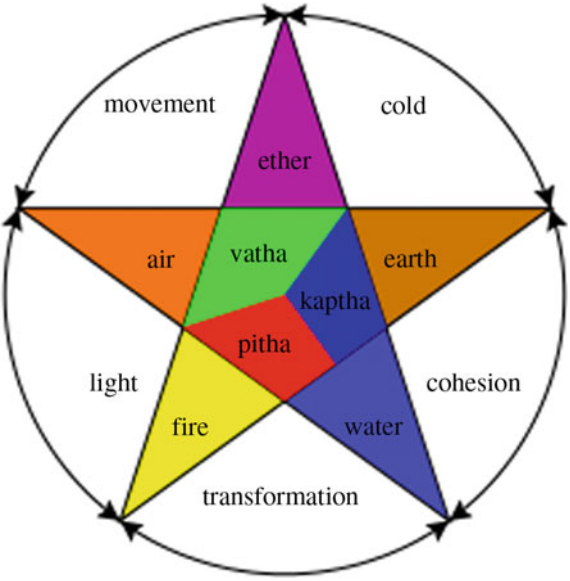


Fig. 3.2 Three doṣhas and the five elements from which they are composed (*Source* https://en.wikipedia.org/wiki/Ayurveda)

strive to create harmony between the body, mind, and spirit, maintaining that this balance prevents illness, treats acute conditions, and contributes to a long and healthy life. Ayurvedic medicine uses a variety of products and practices including herbal compounds, minerals, or metals, special diets, and other unique health practices. The first comprehensive text books on Ayurvedic medicine, the 'CharakaSamhita,' 'Sushruta Samhita,' and Astanga Hridaya, the Great Trilogy, were written in Sanskrit more than 2000 years ago.

Ayurveda recognizes three doṣhas (e.g., Vata, Pitta, and Kapha) and the five elements (e.g., earth, water, fire, air, and ether) from which they are composed (Fig. 3.2). Three biological principles or doshas (type), Vata, Pitta, and Kapha govern all activities of mind and body. Balance is the key factor, and perfect health is a state where mind, body, and spirit are balanced.

The Vata dosha (dry, cold, light, and irregular) is catabolic in function, predominates in the large intestine, and maintains movement in the body (e.g., respiration and joint mobility). The Pitta dosha (hot, wet, oily, light, and intense), metabolic (tissue fueling) in function, predominates in the small intestine. Metabolism, digestive enzymes and glandular secretions (bile) as well as body heat are maintained by Pitta. The Kapha dosha (cold, wet, oily, heavy, slow, and stable) is anabolic in function (tissue building), predominates in the chest and stomach and maintains structure, solidity, and lubrication in the body, forming connective, and musculoskeletal tissues. Vata is mainly air and space, and governs movement in the body—the flow of blood, or elimination, or breathing or thoughts flitting across the mind. Since the other two doshas, Pitta, and Kapha, cannot move without Vata, Vata is considered the lead dosha. Pitta, mainly fire and water, governs heat, metabolism, and transformation. Digestion is an important Pitta activity. Kapha is

made up mainly of earth and water, and accordingly, linked to structure and moisture balance in the physiology. Among other things, Kapha controls weight and lubrication in the lungs, for example. Each of the doshas is also related to a season of the year—Kapha with Spring, Pitta with Summer and Vata with Fall and Winter. Ayurveda names seven basic tissues (dhatu), which are plasma (rasa), blood (rakta), muscles (māmsa), fat (meda), bone (asthi), marrow (majja), and semen (shukra). There are also twenty gunas (qualities or characteristics) which are considered to be inherent in all substances. These are organized in ten pairs of antonyms: heavy/light, cold/hot, unctuous/dry, dull/sharp, stable/mobile, soft/hard, non-slimy/slimy, smooth/coarse, minute/gross, and viscous/liquid.

A balance state of the doshas results in health, while imbalance results in disease. When all the doshas are perfectly in balance in an individual, it means that all the systems and activities of mind and body are functioning at optimal levels, and the individual, therefore, enjoys perfect health. These body constitutions are taken into consideration while treating a patient under this system. In traditional Ayurvedic medicine, health or sickness depend on the presence or absence of a balanced state of the total body matrix including the balance between body, mind, and spirit. Ayurvedic treatments for restoring the balance of disturbed body-mind matrix usually involve the prescribing of herbal medicines, specific diet, and physical activity routines, among other therapies including massage and various purification treatments. Ayurveda has eight ways of diagnosis such as. (i) Nadi (Pulse), (ii) Mootra (Urine), (iii) Mala (Stool), (iv) Jihva (Tongue), (v) Shabda (Speech), (vi) Sparsha (Touch), (vii) Druk (Vision), and (viii) Aakruti (Appearance) (Kurup 2002). Curative treatment in Ayurvedic system consists of administration of medicine both internally and externally, minor surgical operations, and psychosomatic treatment. The medicinal preparations employed in this system are mainly derived from plant materials and are presented in the form of powders, semi-solid preparations, decoctions, elixirs, and distillates. Many of them also contain inorganic chemical substances, minerals, and animal products. Alcoholic extracts and alcoholic solutions of the ingredients, tinctures, and elixirs are also frequently used in Ayurvedic medicine. The *materia medica* of Ayurvedic medicine contains some 8000 published recipes. Ayurvedic medicine uses a variety of products including herbs (*Acorus calamus*, *C. longa*, *Ocimum sanctum*, *Taxus wallichiana*, *Terminalia arjuna*, etc.), metals (gold, silver, copper, lead, tin, iron, zinc, etc.), minerals (sand, lime, Chalcopyrite, Arsenic oxide, Arsenic trisulphide, Arsenic disulfide, Ferric oxide, gems, etc.), animal products (milk, curd, fat, flesh, blood, excretion, hooves, skins, hair, bones, teeth, tusks, etc.), ash (*Bhasma*) from animal derivatives (horns, shells, feathers) containing minerals mixed with herbal extracts (juice or decoction) and some of these products (*Abrus precatorious*, *A. ferox, Boerhavia diffusa*, *Semecarpus anacardium*, *Terminalia chebula*, etc.) may be harmful if used improperly or without the direction of a trained practitioner. The National Center for Complementary and Alternative Medicines (NCCAM) fact sheet indicated that many of the Ayurvedic products contained high levels of lead, mercury, and/or arsenic beyond the acceptable daily intake and, therefore, these products have the potential to be toxic (Saper et al. 2008).

Ayurveda is known as *Astanga Ayurveda* (made up of eight parts). (i) Kayachikitsa (generale medicine), (ii) balachikitsa (pediatrics), (iii) grahachikitsa (psychiatry), (iv) urdhvaangchikitsa (treatment eyes, ears, nose, throat, and head, i.e., above the clavicle), (v) shalyachikitsa (surgery), (vi) visha (toxicology), (vii) jarachikitsa (rejuvenation or gerentorology), (viii) *vajikarana* chikitsa (aphrodisiac and Eugenics therapy), etc., were the eight major branches of ancient Ayurveda. Globalization of Ayurvedic practice has gained momentum in the past two decades. Ayurvedic drugs are used as food supplements in USA, European Union, and Japan (Kurup 2002, 2004). The types of research and developmental activities in Ayurveda undertaken at present include (i) clinical research (clinical trial of ayurvedic preparations) and (ii) drug research (medico-botanical surveys, cultivation of medicinal plants, pharmacognostical studies, phytochemical studies, drug standardization, pharmacological, and toxicological studies). Traditional medicine, including Ayurveda, contributes significantly to the health status of many communities and is increasingly used within certain communities in developed countries.

A large % of people of the Indian subcontinent and other parts of the world use some form of traditional medicine including Ayurveda exclusively or combined with conventional Western medicine (Gogtay et al. 2002; Ni et al. 2002; Kennedy 2005; Saydah and Eberhardt 2006; Alam 2008; Paul et al. 2008; Guneratne 2009).

A review of the use of Ayurveda for cardiovascular disease concluded that the evidence is not convincing for the use of any Ayurvedic herbal treatment for heart disease or hypertension, but that many herbs used by Ayurvedic practitioners could be appropriate for further research (Mamtani and Mamtani 2005). Research into ayurveda has been characterized as pseudoscience. Both the lack of scientific soundness in the theoretical foundations of ayurveda and the quality of research have been criticized (Bausell 2007; Sujatha 2011; Anonymous 2013; Manohar 2013).

Although the researchers have found evidences of the efficacy of Ayurveda in treating various ailments like polycystic ovarian syndrome (Dayani Siriwardene et al. 2010; Khot et al. 2013), rheumatoid arthritis (Chopra et al. 2012), osteoarthritis (Rai et al. 2011), and general health interventions (Conboy et al. 2009), but there prevails a considerable bias opinion against Ayurveda in the Western medical literatures and scientists of repute (but illiterate in Ayurveda), often confuse herbalism and folklore Ayurveda while acknowledging deficiencies in quality control and standardization in the use of herbal medicine(Patwardhan et al. 2004).

Cancer Research UK has found no significant scientific evidence in favor the effectiveness of Ayurvedic medicine against any disease, although massage and relaxation were often beneficial for some cancer patients and there were indications from animal studies that some herbal products used in Ayurveda could be explored further. Some people consider ayurvedic medicine as pseudoscientific on account of its confusion between reality and metaphysical concepts. Other researchers debate whether it should be considered a proto-science, an unscientific, or trans-science system (Quack 2011; Manohar 2009; Anonymous 2013). Although, the evidence in favor of the use of Ayurveda for the treatment of cardiovascular diseases including

hypertension appeared to be inconvincing; but many herbs used by ayurvedic practitioners could be appropriate for further research (Mamtani and Mamtani 2005). Research into ayurveda has been characterized as pseudoscience because of the lack of scientific soundness in the theoretical foundations of ayurveda and so the quality of research has been criticized (Bausell 2007; Sujatha 2011; Manohar 2013).

3.8.3 Traditional Unani Medicine

Unani medicine was originated in ancient Greece around 400 BC. It is a traditional Greco-Arabic medicine, based on the teachings of Greek physician Hippocrates, Dioscorides, and Galen (the forerunners of Western herbal medicine and founders of Unani medicine), and was developed into an elaborate medical system in middle age by the Muslim physicians like Al-Razi, IbnSena, Al-Zahrawi, and IbnNafis. Unani medicine first arrived in India around thirteenth century with establishment of Delhi Sultanate and flourished under Mughal Empire. The Unani system has grown out of the fusion of the traditional knowledge of ancient civilizations like Greek, Egypt, Arabia, Iran, China, and India. The system of medicine was documented in Kitab al-Mansuri by Al-Razi (850–925 AD), in Al-Kanun by Ibn Sina (980–1037 AD), and in many other books written by the Unani physicians. Unani explains that human consists of three parts with same weight, viz. solid part (organs), liquid part (body fluid), and gaseous part (spirit). According to the Unani system, the basic factors composing the human physique are four elements (fire, air, water, and earth), four

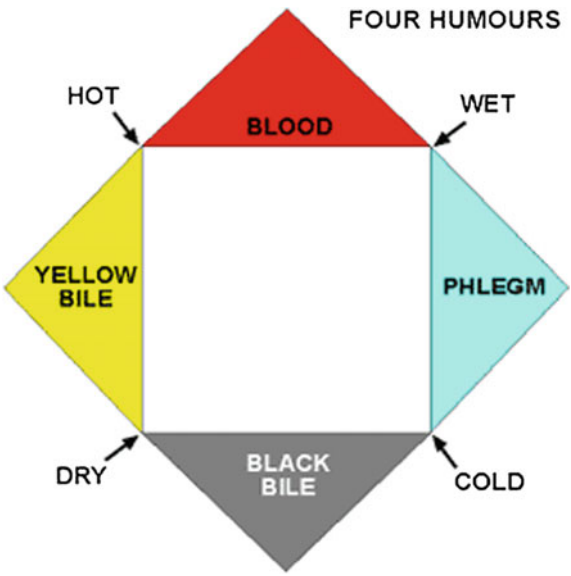


Fig. 3.3 Basic factors composing the human physique: four elements (earth, air, water, and fire); four natures (cold, hot, wet, and dry), and four humors (blood, phellem, yellow bile, and black bile) of the Unani system (*Source* http://www.itmonline.org/arts/unani.htm)

types of temperament (hot and dry, hot and wet, cold and dry, and cold and wet); body liquid is composed of four humors (blood, phlegm, yellow bile, and black bile), four faculties, organs, and parts, vital principles (respiratory, circulation, and immune systems), powers and functions (Fig. 3.3). According to Unani philosophy, the health and illness of a person depend upon the balance or equilibrium of four humors in the body, and if balance or equilibrium of the humors is disturbed, disease sets in. Restoration of balance in body humors is necessary to heal diseases. The Unani system involves four elements: earth, air, water, and fire; along with four natures: cold, hot, wet, and dry; and four humors: blood (which is hot/wet), phlegm (cold/wet), yellow bile (hot/dry), and black bile (cold/dry). Thus, the Unani system (with four elements) differs from the Ayurvedic system of three doshas and the Chinese system of five elements.

Unani treatments for restoring equilibrium and normal body functions involve the prescribing of herbal and mineral medicines, specific diets as well as exercise, massage, and Turkish baths, among other therapies. Unani system of medicine has been found to be efficacious in conditions like rheumatic arthritis, jaundice, filariasis, eczema, sinusitis, and bronchial asthma. Treatment in Unani consists of three components, viz. preventive, promotive, and curative. For the prevention of disease and promotion of health, the Unani system emphasizes six essentials: (a) pure air (b) food and water (c) physical movement and rest (d) psychic movement and rest (e) sleep and wakefulness, and (f) retention of useful materials and evacuation of waste materials from the body. There are four forms of treatment in Unani medicine including pharmaco therapy (medication), dietotherapy, regimental therapy (manipulative), and surgery. Regimental therapy is a special technique/physical method of treatment to improve the constitution of body by removing waste materials and improving the defense mechanism of the body and protect health. According to Unani medicine, any disease should be treated based on the diagnosis. Several factors including signs, symptoms, test results, and mental status should be considered with importance in diagnosis. Once the diagnosis is made, management strategy depending on the diagnosed disease should be decided based on etiology, including removal of the causal factor, normalization of the body fluid, and normalization of tissue or organs. Whole plants or their powders or pastes or products and their extracts, infusions, decoctions, and distillates are major constituents of Unani medicine. Minerals, inorganic chemicals, and animal products are also frequently used in preparing these medicines. However, tinctures or elixirs (which are alcoholic preparations) are not used in Unani medicine. Traditional Unani medicine is practiced today in many Middle Eastern and South Asian countries including Bangladesh, India, Pakistan, and Sri Lanka. The Unani concept of body fluid became the basis of Christian medicine of the middle Ages, subsequently transferred to USA and many regions of Mexico and Latin America by settlers from England and Spanish-Portuguese conquerors, respectively. References mentioning Unani medicine can be found extensively through the whole world.

3.8.4 Homoeopathy

Homoeopathy is a system of alternative medicine created in 1796 by Christian Friedrich Samuel Hahnemann based on the concept of like cures like, e.g., a substance that causes to develop symptoms of a disease in healthy person will cure disease of similar symptoms of a sick person. Homoeopathy is a method of treating diseases by administering drugs which have been experimentally proved to possess the power to produce similar symptoms on healthy human beings. The physicians from the time of Hippocrates at about 400 BC have observed that certain substances could produce symptoms of a disease in healthy people similar to those of people suffering from the disease. CFS Hahnemann (1755–1843), a German physician, came to know from a materiamedica that *Cinchona* bark was effective in treating malaria because of its astringency and began to research *Cinchona*'s effect on the human body by self-application. The drug induced malaria-like symptoms in him and he claimed that it would do so in any healthy individual. This led him to postulate a healing principle, like cures like (similia similibus curentur), and gave the name homeopathy. He first used the term homeopathy in his essay: 'Indications of the homeopathic employment of medicines in ordinary practice,' published in Hufeland's Journal in 1807 (Gumpert 1945). Like cures like (i.e., law of similar), law of the infinitesimal dose (i.e., the more dilute the remedy, the greater its potency), and holistic treatment (i.e., an illness is specific to the individual) were three principles upon which homoeopathy was formulated.

Homoeopathy is based on the assumption that the causation of a disease mainly depends upon the susceptibility or proneness of an individual to the incidence of the particular disease in addition to the action of external agents like bacteria, viruses, etc. Treatment in homoeopathy is holistic in nature and focuses on an individual's response to a specific environment. Homoeopathy has its own areas of strength in therapeutics, and it is particularly useful in treatment for allergies, bronchial asthma, autoimmune disorders, diabetes, arthritis, epilepsy, skin eruptions, mental or emotional disorders, and viral infections. Many surgical, gynecological, and obstetrical and pediatric conditions and ailments affecting the eyes, nose, ear, teeth, skin, sexual organs, etc. are amenable to homoeopathic treatment. Behavioral disorders, neurological problems, and metabolic diseases can also be successfully treated by homoeopathy. Homoeopathy can also be useful for de-addiction from drugs, tobacco, and alcohol. Apart from the curative aspects, Homoeopathic medicines are also used in preventive and promotive health care. In recent times, there is an emergence of interest in the use of homoeopathic medicines in veterinary care, agriculture, dentistry, etc. Homoeopathic medicines are prepared mainly from natural substances such as plant, animal, and minerals sources. Remedies (liquid, tablet or powder form) are prescribed in accordance with a patient's symptoms and health conditions while individual characteristics such as emotions and physical condition are also taken into account. Homeopathic medicines are prepared different sources, e.g., from medicinal plants ($\sim$60%), minerals ($\sim$20%), and a few from animals, diseased tissues (nosodes), hormones

and healthy tissues (sarcodes), as well as certain imponderables energy sources are used to prepare homeopathic medicines. Plant-derived medicines in this system are used as mother tinctures. No excipient (preservative, color, sweetener, flavor, etc.) is used in preparing homeopathic medicine.

The whole plant or parts of it (e.g., leaf, root, flower, seed, and berry) are used in the preparation of homeopath medicines. *Pulsatilla nigra, Bryonia alba, Aconite napellus, Gelsemium, Coffea cruda, Rhus toxicodendron,* etc. *Achillea millefolium*, *Aconitum ferox*, *Cephaelis ipecacuanha*, *Quassia amara*, *D. stramonium*, *Argemone ochroleuca*, *A. belladonna*, *A. calamus*, *Anthemis nobilis* and *S. nux-vomica* are a few examples of plant species used in homeopathy. Minerals (metals, non-metals, and their salts) used in the preparation of homeopathic medicines include Aurum metallicum (gold), Cuprum met (copper), Ferrum met (iron), Kali carbonicum (potassium), Natrum muriaticum (common salt), Bromine (Br), Iodium (Iodine), Phosphorus (P), Sulfur (S), calc phos, calc carb, Lithium carb, natrum sulph, kali phos, graphites, mica, and silica (sand). Organic acids (acetic acid, benzoic acid, salicylic acid, carbolic acid, citric acid, and formic acid), mineral oils (kerosene, paraffin), wood distillates (camphor, kreosote), etc., are also used as homeopathic medicines.

Products from animal sources such as snake (*Naja naja,* Vipera *lachesis*); spider (*Aranea avicularis*, *Tarantula Hispania*); cockroach (*Blatta americana*, *B. orientalis*), snails (*Helix pomatia*), dry Spanish fly, *Bufo rana* excretion (bufo); sarcodes (products of animal glands and endocrine glands), nosodes (morbid product) including *Ambra grisea* (morbid products of whale), anthracinum (anthrax poison), aviare (tuberculin virus), hydrophobinum or lyssin (saliva of a rapid dog), malandrinum (grease in horse), and similar other products are used in the preparation of homeopathic medicine. The homeopathic practitioners initiated the use of nosodes containing bacteria, viruses, and other microorganisms in miniscule amounts (e.g., *Tuberculinum, Syphilinum,* and *Variolinum*) as medicines long before the introduction of vaccines. Medicines (imponderabilia) prepared from immaterial energy (natural or artificial) including Luna (full moon), magnetis poli ambo (magnet), magnetis polus australis, and magnetis polus arcticus (south- and north-pole of a magnet), Radium bromatum (Rad-br), sol (sun rays) as well as X-ray, electricitus, etc., are also considered in homeopathic treatment.

Homeopathic medicines are essentially nano-medicines because only miniscule amounts of the original drug substance are used and therefore they do not cause any adverse effect (toxic, poisonous or side effects). It differs from other systems of medicine by its unique method of potentization (dilutions of the original substance are called potencies) and Hahnemann discovered that the more a substance was potentized (or diluted), the less often it needed to be administered to the patient to create a remedial action and the deeper was its result. There are two commonly used dilution scales, X or decimal (1 part plant extract: 9 part alcohol or other carrier) and C or centesimal (1 part plant extract: 99 part alcohol or other carrier). Homeopathic medicines are available in certain standard potencies such as 30c, 100c, 200c, 1000c, 10K, and 50K. The usual convention in homeopathy is to refer to the higher dilutions, indicated by the larger numbers and higher potencies and the

lower dilutions, indicated by smaller numbers and lower potencies. It seems odd to a lay man since the higher dilutions contain less of the original medicinal substance but homeopaths believe that the higher dilutions elicit powerful responses in patients. Pulsatilla 30C has undergone 30 steps of dilution, each step having been a one-to-one-hundred dilution. Homeopathy is economical as well and has a very broad public acceptance.

In spite of all these facts (no adverse effect, cheap, easily available, broad public acceptance, etc.), homeopathy system of medicine is often badly criticized. Homeopathy is considered a fake system treatment and pseudoscience, it lacks biological plausibility, and its remedies have been found to be no more effective than placebos. Dilution appears to continue well past the point where no molecules of the original substance remain. Continued homeopathic practice, despite the evidence that it does not work, has been criticized as unethical because it increases the suffering of patients by discouraging the use of real medicine (Shaw 2010), and the WHO gave warning against using homeopathy to try to treat severe diseases such as HIV and malaria (Mashta 2009). Homoeopathy was brought to Indian subcontinent about 1810 AD by European missionaries. This system of medicine is very popular in many Asian countries including Bangladesh.

3.8.5 Aromatherapy

Aromatherapy (or essential oil therapy) is the treatment or prevention of disease including pain and anxiety reduction, enhancement of energy and short-term memory, relaxation, hair loss prevention, and reduction of eczema-induced itching by the use of essential or volatile oils. Essential oils, the pure essence of a plant, have been found to provide both psychological and physical benefits when used correctly and safely. Fragrance oils and perfume oils contain synthetic chemicals and do not provide the therapeutic benefits of essential oils. Essential oils from different plant sources have been found to posses various degrees of antimicrobial, anti-viral, nematicidal, antifungal, insecticidal, and antioxidant properties. Two basic mechanisms are offered to explain the purported effects, e.g., (i) the influence of aroma or essential oils may influence the brain, especially the limbic system through the olfactory system; and (ii) the effects of essential oils may be direct and pharmacological.

Aromatherapy employs various plant materials and aromatic plant oils, including (i) essential oils (e.g., eucalyptus oil, grapefruit oil, incense reed diffusers; the essential oil profiles area details <90 essential oils); (ii) absolutes (e.g., rose absolute, fragrant butters, concretes, enfleurage pommades); (iii) carrier oils (e.g., sweet almond oil); (iv) herbal distillates (e.g., rosewater, chamomile, rose, and lemon balm); (v) infusions (e.g., infusion of chamomile); (vi) phytoncides consisting of various volatile organic compounds (many terpene-based fragrant oils and sulfuric compounds from *Allium* spp. are phytoncides, but less commonly used in aromatherapy due to their disagreeable odors); (vii) aroma lamp or vaporizer; and

(viii) other miscellaneous aroma compounds and natural ingredients (e.g., cold pressed vegetable oils, jojoba—a liquid wax, herbs, milk powders, sea salts, sugars —an exfoliant, clays, and mud) for improving psychological or physical well-being.

Different essential oils have different uses and effects, e.g., basil essential oils is used to sharpen concentration, alleviate symptoms of depression, and relieve headaches and migraines; bergamot oil is useful for the urinary tract and digestive tract, and in combined with eucalyptus oil relieves skin problems, including those caused by stress and chicken pox; black pepper oil is commonly used for stimulating the circulation, muscular aches and pains, and bruises, and when combined with ginger essential oil, it is used to reduce arthritis pain and improve flexibility; chamomile essential oil is applied in treatment of eczema; citronella oil acts as an insect repellent; clove oil possesses antimicrobial, antioxidant, and antifungal properties, acts as topical analgesic, or painkiller (commonly used for toothache and also used as an antispasmodic antiemetic), prevents vomiting and nausea, and as a carminative, prevents gas in the gut; eucalyptus oil relieves the airways during a cold or flu; geranium oil can be used for skin problems, reduces stress, and functions as a mosquito repellant; jasmine oil is an aphrodisiac; lavender oil is used as an antiseptic for minor cuts and burns and to enhance relaxation and sleep, relieves headache and migraine symptoms; lemon oil improves mood, relieves the symptoms of stress and depression; rosemary oil promotes hair growth, boosts memory, prevents muscle spasms, and supports the circulatory and nervous systems; sandalwood oil is aphrodisiac; tea tree oil is antimicrobial, antiseptic, and disinfectant (commonly used in shampoos and skin care products), and used also to treat acne, burns, and bites; thyme oil helps to reduce fatigue, nervousness, and stress; and yarrow oil is used to treat symptoms of cold and flu, and to treat joint inflammation.

Aromatherapy utilizes blends of therapeutic essential oils and the modes of application include that can be issued through topical application (for general massage, baths, compresses, therapeutic skin care), inhalation (for respiratory disinfection, decongestant, expectoration as well as psychological effects), aerial diffusion (for environmental fragrancing or aerial disinfection) or water immersion to stimulate the desired response. Inhaling essential oils stimulates the olfactory system, the part of the brain connected to smell, including the nose and the brain. As the molecules reach the brain, they affect limbic system and the limbic system is linked to the emotions, the heart rate, blood pressure, breathing, memory, stress, and hormone balance. It is assumed that the essential oil therapy, in this way, brings about positive holistic effect on the body. During topical application through massage oils, medicaments are absorbed through the skin and boost circulation and thereby cure the affected area. Essential oils are never applied directly to the skin, they must be diluted with carrier oil (sweet almond oil or olive oil) and an allergy test should be done before trying a new essential oil. Aromatherapy is a complementary therapy or as a form of alternative medicine. It does not provide a cure for diseases, rashes, or illnesses, but it can support conventional treatment of various conditions. It helps to reduce a number of ailments (e.g., nausea, pain, and body aches; anxiety, agitation, stress, depression, fatigue, and insomnia; headaches and

circulatory problems; menstrual and menopausal problems; alopecia, or hair loss; some types of psoriasis). Although aromatherapy be offered as a complementary therapy or as a form of alternative medicine, but there is no good medical evidence that aromatherapy can either prevent or cure any disease, but it might help improve general well-being (Ades 2009; Hines et al. 2012). Evidence for the efficacy of aromatherapy in treating medical conditions is poor (Edris 2007; van der Watt and Janca 2008).

3.8.6 Traditional Siddha Medicine

Siddha system of medicine (SSM) is one of the oldest systems of medicine in Indian subcontinent. The term Siddha means 'achievements,' and Siddhars were saintly persons who achieved 'results' in medicine. It is not well circulated among the scientific community compared to other traditional systems such as Ayurveda, Unani, TCM, and Kampo. SSM is confined to the Tamil-speaking part of India. The Siddha system of medicine emphasizes that medical treatment is oriented not merely to disease but has to take into account the patient, the environment, age, sex, race, habits, mental frame, habitat, diet, appetite, physical condition, physiological constitution, etc. This means the treatment has to be individualistic and ensures a low probability of incorrect diagnosis or treatment. The diagnosis of diseases in Siddha involves identifying its causes through the examination of eight sites including pulse, eyes, voice, color of body, touch, tongue, the status of the digestive system (faeces), and urine. The system has developed a rich and unique treasure house of drug knowledge in which use of metals and minerals is liberally made. Siddha medicines containing mercury, silver, arsenic, lead, and sulfur have been found to be effective in treating certain infectious diseases including venereal diseases. The Siddha system is effective in treating chronic cases of liver, skin diseases, especially psoriasis, rheumatic problems, anemia, prostate enlargement, bleeding piles, peptic ulcer, and even psychiatric diseases.

The resources of SSM have been categorized into three groups such as (i) plant products, (ii) inorganic substances (e.g., mercury, silver, arsenic, lead, sulfur), and (iii) animal products (e.g., human and canine skulls 'ash-*chunnam*) and they are characterized by means of taste, quality, potency, specific action, etc. A few of the SSM plants are *Acalypha indica, Adhatoda vasica, A. barbadensis, Apium graveolens, A. indica, B. diffusa, Borassus flabellifer, Caesalpinia bonduc, Calotropis gigantea, Crocus sativus,* C*uminum cyminum, Cynodon dactylon, Euphorbia hirta, O. sanctum, Piper longum, P. nigrum, Phyllanthus amarus, Phyllanthus emblica, Solanum nigrum, S. trilobatum, S. xanthocarpum, Strychnos potatorum, W. somnifera, Zinger officinale*, etc.

In the divine method, medicines are prepared from minerals, in the rational method; medicines are prepared from herbs and in surgical method, incision, excision, bloodletting, and heat application, leech application, etc. are practiced. Medicines containing mercury, silver, arsenic, lead, sulfur, etc. appear to be toxic

although they are effective in treating certain infectious diseases. Purgative, emetic, fasting, steam, oleation, physical, solar, yoga, etc. therapies are some of the examples therapeutic treatments in Siddha.

3.8.7 Yoga

Yoga is primarily an oriental way of life form. Once it was confined to hermits, saints, and sages but now it has taken its place in everyday life and has aroused a worldwide awakening and acceptance. Yoga is a primitive, preventive, and curative intervention. It consists of eight components viz., restraint, observance of austerity, physical postures, breathing exercise, restraining of sense organs, contemplation, meditation, and samadhi. These steps in the practice of Yoga have the potential to improve social and personal behavior and to improve physical health by encouraging better circulation of oxygenated blood in the body, restraining the sense organs and thereby inducing tranquility and serenity of mind. A number of postures are described in Yogic works to improve health, to prevent diseases and to cure illness. The physical postures are required to be chosen judiciously and have to be practiced in the correct way so that the benefits of prevention of disease, promotion of health, and therapeutic use can be derived from them. The practice of Yoga has also been found to be useful in the prevention of certain psychosomatic disorders or diseases and improves individual resistance and ability to endure stressful situations. Yogic practice assumes to improve intelligence and memory and help in developing resistance to situations of strain and stress and also help individual to develop an integrated personality. Meditation can stabilize emotional changes and prevent abnormal functions of the vital organs of the body such as restrains the sense organs and controls the nervous system.

3.8.8 Naturopathy

Naturopathy is a drugless, non-invasive therapy involving the use of natural materials in its treatment based on the theories of vitality, toxemia, self-healing capacity of the body, and the principles of healthy living. Naturopathy is a scientific system of healing, stimulating the bodys' inherent power to regain health with the help of five great elements of nature—Earth, Water, Air, Fire, and Ether. The advocates of Naturopathy pay particular attention to eating and living habits, adoption of purificatory measures, use of hydro-therapy, cold packs, mud packs, baths, massages, fasting etc. Naturopathy is a system of treatment as well as a way of life-living in harmony with constructive principles of Nature on the physical, mental, moral, and spiritual planes. It is a call to return to nature and to resort to a simple way of living in harmony with the self, society, and environment, advocating better health without medicines. It has great promotive, preventive, curative

as well as restorative potential. It is very effective in chronic, allergic, and stress-related disorders. The theory and practice of Naturopathy are based on a holistic view-point. It is widely practiced, globally accepted, and recognized by the World Health Organization.

3.8.9 Folk Medicine

Folk medicine is a simple form of traditional medicine as practiced by people isolated from modern medical services involving the use of plant, animal, and other natural-derived remedies on an empirical basis from time immemorial. Organic, psychic, and social phenomena are strangely intermingled in folk medicine. Folk medical practice, a simple form of traditional medical practice, offers healthcare services to the rural people with or without the use of medicinal preparations. Folk medicine consists of both material and non-material components. The material components consist of medicinal preparations from plants and animal products. These are dispensed usually in their raw forms and are used in treating simple diseases like cold, cough, fever, indigestion, constipation, diarrhea, dysentery, intestinal worms. The non-material components consist of religious and spiritual items. The religious items include: (i) religious verses from holy books are either written on papers and given as amulets, or encapsulated into small size metallic capsule or box followed by wax seal to make airtight for wearing on body; or recited and blown on the face or body of the patient, or on water to be drunk, or on food to be eaten, or on string to make knots and the to be fastened around arms, necks or waist; and (ii) sacrifices and offerings given in the name of God and deities. Belief of the rural people regarding disease causation includes several mythological perceptions including God's will, divine punishment for wrong doing, improper food intake, influence of an evil eye or spirit etc. It is widely believed in rural areas including a large section of urban society that one has to take the help of mystic powers to treat diseases and the mystic power comes from *fakir*, *pir*, *maulavi*, and similar others. Common traditional treatments include *panipara* (water incantation), *jharphook* (oral incantation), *tabij* (sacred amulet), and *telpara* (oil incantation). Spiritual items include communicating with spirits or ancestors through human media to inquire about the disease and its remedy, recitation of incantations to drive away imaginary evil spirits, and many other similar methods. Non-material components, either independently or in combination with material components, are generally applied in the treatment of all kinds of diseases, but are specifically used in the treatment of patients with psychological problems such as insanity, various types of phobias, and depression and fear of supernatural creatures. Sometimes their use extends to the treatments of diseases like pox, cancer, leprosy, fractures, snakebite, and even tetanus in newly born children.

A practitioner in herbal medicine not registered or not having any formal medical education is locally called a *kabiraj*. He prepares the medicine himself from

locally available herbs and usually keeps the formula a secret. The formula is either inherited or self manufactured or received from a master (*ustad*). Religious practitioners are invited to perform exorcism whenever a person is possessed by a *zin* or *bhut* (spirit). Too often, religio-magical practices go beyond the level of health-seeking behavior to explain minor vices and crimes. To find out a thief or to isolate an offender different magical techniques are used. *Aynapara* (sanctified mirror), *batichalan* (throwing an incantated bowl), *lathi* or *chatachalan* (sanctified bamboo stick or peel) etc., are used for tracing out a thief, or finding out the amulets utilized by malicious persons to put a curse on someone. Magical practitioners take recourse to incantation. They are called *bede* or *ozha* and are invited to perform exorcism whenever a person is bitten by a snake or has diseases such as pain, rheumatism, toothache. In Bangladesh, there are several categories of folk medicines including non-registered herbal, magical, and magico-religious. Despite the availability of the modern medicine, folk medicine still occupies a dominant place, especially in the rural society.

3.8.10 Traditional North American Medicine

Traditional Native American Medicine is a general term for the systems of healing used by all Native American nations or tribes that have been practiced in some cases for at least 10,000 years. Some estimates suggest the first medical practices of the North American tribes began at some 40,000 years ago. Native American medicine is a collective of the old healing practices, herbal cures, and other remedies of the North American tribes. These were gathered and passed orally from one generation to the next and over time, the various treatment methods of the different tribes were integrated. It is now difficult to trace the origin of a specific healing technique. There were more than 2000 tribes of indigenous people in North America and the healing practices these tribes varied widely involving various rituals, ceremonies, and a diverse wealth of healing knowledge. In Canada, it is also known as aboriginal traditional medicine. For thousands of years, Native Americans have used herbs to heal the body, purify the spirit, and bring balance into their lives and their surroundings. So in Traditional Native American Medicine, due consideration is given on the role of spirituality in the healing process as they believe that all things in nature are connected and that spirits can promote health or cause illness. Accordingly, the healing of physique of an individual needs emotional wellness, harmony with community and the surrounding environment. In contrast to present day modern medicine (which focuses only on science and the mechanistic view of the body), the Native Americans continue to include the spirit as an inseparable element of healing.

All three traditional systems of medicine such as Native American, traditional Chinese medicine (TCM), and Ayurvedic followed the same basic principle in healing although they were distantly separated by space, time, and culture. Traditional Native American medicine like two other ancient healing systems (e.g.,

Ayurveda and TCM) is holistically linked to philosophy, lifestyle, emotions, social setting, natural surroundings, religion, and spirituality, and treatments aim to balance the physical, emotional, mental, and spiritual components of a person. Most systems of Native American Medicine involve a tribal healer, also known as a medicine man or medicine woman, and may also involve the patient's family or entire community to help an ill person in ceremonies, dances, etc. Treatments include prescribing medicinal herbal preparations, ritual purification or purging, traditional smudge or burning of certain herbs, as well as chanting, dances, and prayers.

There were no written records of herbal use by the indigenous people of America prior to the arrival of the first European settlers and the indigenous people then shared their knowledge with the new settlers. Hundreds of medicinal herbs were used in Native American remedies. Tobacco was used in healing numerous ailments, in rituals and ceremonies. Sage was also important healing herb to Native Americans for multiple problems of the stomach, colon, kidneys, liver, lungs, skin, etc., and it was also used to protect against bad spirits. Other remedies for common colds include American Ginseng or Bonset; herbs for aches and pains including wild black Cherry, Pennyroyal, and Hops; remedies for fever, including Dogwood, Feverwort, and Willow bark.

3.8.11 Traditional Western Herbal Medicine

Traditional Western herbal medicine has a long history, with the roots of its practice found in the writings of the Greek and the Romans physicians (Hippocrates, Dioscorides, Galen). Like other systems of traditional herbal medicine (THM), the use of medicinal plants in the treatment and prevention of disease, as well as in the maintenance of health, is fundamental to the practice of Western THM. In Western THM, medicinal herbs are prescribed in the context of a Western understanding of health and disease. The 'Western' THM encompasses a number of similar, but unique and separate systems of herbal medicine. In Europe, for example, each country has evolved its own form of THM, largely because of language and social differences. Western THM embraces the approaches of European herbalists, as well as those in North America, Australia, and New Zealand. The formalized systems of Western THM have two elements that have merged to form our modern understanding. The first element comes from the oral tradition of folk herbalism. For example, the use of foxglove in treating heart failure was developed from the observation of successful treatments of dropsy by a village wise-woman in the eighteenth century. Secondly, there is clinically based science of herbal medicine. This essentially means that the Methods and practices of our scientific approach to medicine have been applied to the study of herbal medicine. In this way, the practice of herbal medicine has contributed to the knowledge of conventional modern medicine. Western herbal medicine includes herbs of both Western and Oriental origin (St. John's wort, gotu kola, Ginkgo biloba, bilberry,

dandelion, echinacea, ephedra-ma huang, flaxseed oil, garlic, ginseng, green tea, horse chestnut, kava, melatonin, mistletoe, and saw palmetto), relies on the potential synergistic and curative properties of plants to treat a particular symptom or disease or to enhance overall wellness. Western herbalism is also based upon pharmacognosy, the study of natural products, including the identification, extraction methods, and applications of specific plant constituents responsible for therapeutic actions (e.g., digoxin is extracted from Digitalis leaf and used in the treatment of heart failure) and herbs of the Western herbal medicine tradition are now researched extensively for various medicinal uses (e.g., garlic has been researched as a potential treatment for high blood pressure).

3.9 Use of Medicinal Plants in Complementary and Alternative Medicines (CAMs)

The field of complementary and alternative medicine, the non-mainstream medicine i.e., not part of standard medical care, is known as CAM. Alternative medicine is any practice that is put forward as having the healing effects of medicine, but is not founded on evidence gathered using the scientific method. It consists of a wide range of healthcare practices, products, and therapies such as homeopathy, naturopathy, chiropractic, magnetic field therapy, energy medicine, various forms of acupuncture, Traditional Chinese medicine, Ayurvedic medicine, Christian faith healing, and many others that are not part of the science based healthcare system. Complementary medicine is used together with conventional or modern medical treatment in a belief that it 'complements' the treatment while alternative medicine is used alone without modern medicine. Integrative medicine (or integrative health) is the combination of the practices and methods of alternative medicine with modern medicine. Alternative medical diagnoses and treatments are usually not included in the degree courses of medical education. Unlike modern medicine, alternative therapies lack scientific validation, and their effectiveness is not proved clinically. Methods may be based on traditional medicinal practices of a particular culture, folk knowledge, supersition, spiritual beliefs, belief in supernatural energies (anti-science), pseudoscience, errors in reasoning, propaganda, fraudulence, new or different concepts of health and disease, and may incorporate any bases other than being proven by scientific methods. Regulation and licensing of alternative medicine and healthcare providers vary from country to country. CAM is not as well researched as modern medicine which undergoes intense research before being released to the public. Critics and also the scientific community have criticized alternative medicine as being based on misleading statements, quackery, unscientific beliefs or traditional practices. It is an issue of non-maleficence. However, complementary medicine is used together with standard medical care, e.g., acupuncture holds promise for relieving vomiting following cancer chemotherapy.

Similarly, alternative medicine is used in place of standard medical care, e.g., treatment of heart disease with the help of chelation therapy that removes excess metals from the blood instead of a standard approach. Evidence suggests that acupuncture also may ease some chronic pain conditions, including headaches, low back pain, and osteoarthritis of the knee. There is research to show that some CAM techniques can help with problems like pain and nausea. But other alternative therapies do not have enough medical evidence to determine if they are effective. The boundaries between complementary and conventional medicine overlap and change with time. For example, guided imagery and massage, both once considered complementary or alternative, are used regularly in some hospitals to help with pain management. Cancer treatment centers with integrative healthcare programs may offer services such as acupuncture and meditation to help manage symptoms and side effects for patients who are receiving conventional cancer treatments such as chemotherapy.

3.10 Modern Medicine

Modern medicine refers to mainstream, conventional, orthodox or allopathic medicine. Allopathic medicine is also called Western medicine, biomedicine, regular medicine, or evidence-based medicine. It is evidence-based practice for diagnosing and treating disease. Mainstream medicine assumes that all physiologic and pathological phenomena can be explained in concrete terms, and 'best practice' is the end result of a stream of objective analyses which begin with non-human model systems, evolve through blinded studies and statistical analysis of those results, and end with guidelines to which doctors adhere to achieve optimal patient outcomes. Allopathic medicine and allopathy are terms coined in the early nineteenth century (1810) by Samuel Hahnemann, the founder of homeopathy, as a synonym for mainstream medicine. Modern medicine is practiced by holders of MD (medical doctor) or DO (doctor of osteopathy) degree holders and by their allied health professionals, such as physical therapists, psychologists, and registered nurses. Before the twentieth century, most medicines were extracted from plants (herbal medicines). Since 1900, thousands of modern drugs have been synthesized from organic compound. Modern medicines can be classified based on their effects on the human body as analgesics, antibiotics, psychotherapeutic drugs etc. Modern medicines usually contain a mixture of active ingredients prepared in different forms, such as capsules, pills, solutions or suspensions. For example, Alka-Seltzer (used as an antacid) contains sodium bicarbonate, citric acid, and aspirin. It is the sodium bicarbonate then neutralizes the excess stomach acid. Modern drugs have a trade name and a generic name. For example, the analgesic aspirin (generic name) is sold under different brand names such as Caprin and Disprin. Similarly, paracetamol (generic name) is sold under the trade name of Panadol.

3.11 Scientific Basis of Herbal Medicine and Its Merits and Demerits

Herbal medicine remains largely an unproven, inexact science. Although the history of herbal medicine provides several decades or centuries of anecdotal information, scientific study of herbal medicine remains in its infancy. For example, the US Department of Health and Human Services, National Center for Complementary and Alternative Medicine (NCCAM) has only been in operation since 1992. Compared to the Federal Food and Drug Administration (FDA), which was founded over 100 years ago, NCCAM is in its infancy and has only begun to scratch the surface of scientific research.

Despite the criticism of herbal medicine among mainstream medical professionals, it is wise to remember that many common drugs in use today were derived from plant-based sources. Scientists originally derived aspirin from willow bark; herbalists prescribe white willow for headaches and pain control. Digitalis, a drug prescribed for certain heart conditions, comes from an extract of potentially toxic foxglove flowers. While it is true that herbal supplement manufacturers often make bold or outrageous claims, critics should not be so quick to dismiss herbal medicine as quackery.

3.11.1 Advantages and Disadvantages of Herbal Medicine

There are numerous advantages and disadvantages of herbal medicine.

Advantages of Herbal Medicine

a. The advantages of using herbal medicines are numerous. Herbal medicines tend to be more effective for long-standing health complaints that do not respond well to traditional medicine. Herbs typically have fewer side effects and may be safer to use over time.
b. An example may be seen with herbs and alternative remedies used to treat arthritis. Vioxx (rofecoxib), a well-known prescription drug uses to treat arthritis, was recalled due to increased risk of cardiovascular complications. Alternative treatments for arthritis, on the other hand, have few side effects. Adjusting the diet to remove vegetables from the nightshade family, reducing white sugar consumption, and adding simple herbs to the diet have few side effects. Most herbal medicines are well tolerated by the patient, with fewer unintended consequences than pharmaceutical drugs.
c. Another advantage to herbal medicine is cost. Herbs cost much less than prescription medications. Research, testing, and marketing add considerably to the cost of prescription medicines. Herbs tend to be inexpensive compared to drugs.
d. Yet, another advantage of herbal medicines is their availability. Herbs are available without a prescription, and some simple herbs, such as peppermint and

chamomile, can be grown at home. In some remote parts of the world, herbs may be the only treatment available to the majority of people. Many find the easy availability of herbs appealing.

Disadvantages of Herbal Medicine

a. Herbs are not without some disadvantages. For sudden, serious illnesses, mainstream medicine still reigns supreme. An herbalist would not be able to treat serious trauma, such as a broken leg, nor would he be able to heal appendicitis or a heart attack as effectively as a conventional doctor using modern diagnostic tests, surgery, and drugs. Modern medicine treats sudden illness and accidents much more effectively than herbal or alternative treatments.
b. Another disadvantage of herbal medicine is the very real risks of doing oneself harm through self-dosing with herbs. While one can argue that the same thing can happen with medications, such as accidentally overdosing on cold remedies, many herbs do not come with instructions or package inserts. There is a very real risk of overdose.
c. Harvesting herbs in the wild are risky, if not foolhardy, yet some people try to identify and pick wild herbs. They run a very real risk of poisoning themselves if they do not correctly identify the herb, or if they use the wrong part of the plant.
d. Herbal treatments can interact with medications. Nearly all herbs come with some warning, and many, like the herbs used for anxiety, such as Valerian and St. John's Wort, can interact with prescription medication such as antidepressants. It is important to discuss medications and herbal supplements with qualified doctor.
e. Because herbal products are not tightly regulated, consumers also run the risk of buying inferior quality herbs. The quality of herbal products may vary among batches, brands, or manufacturers. This can make it much more difficult to prescribe the proper dose of an herb.

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Chapter 4
Drugs: Their Natural, Synthetic, and Biosynthetic Sources

Abstract The term 'drug' was derived from the French word 'drogue' or dried herbs, and a crude drug is any naturally occurring unrefined substance derived from biological or mineral sources intended for use in the diagnosis, cure, mitigation, and prevention of diseases. A crude drug contains pharmacologically active ingredients and requires no additional processing for use, e.g., ginseng (*Panax* spp.) root, dry leaf of *Digitalis* spp., dry root of rhubarb (*Rheum rhabarbarum*), leaves and flowering tops of peppermint (*Mentha piperita*), bark of cascara (*Rhamnus purshiana*), dried milk juice of opium (*Papaver somniferum*), and whole dried insect like Spanish fly (*Lytta vesicatoria*). An official drug is included in pharmacopoeia or in national formulary or in recognized books like pharmacopoeia, national formulary or pharmaceutical codex, e.g., quinine, morphine, codeine, paracetamol are included in BP (British pharmacopoeia); an unofficial, a drug that was recognized earlier in the pharmacopoeia but deleted from the current issue due to severe toxic effects on humans, e.g., sucralfate (hyperacidity), mercurial compounds (diuretics), benzoic acid (preservative), while a drug that did not appear in either of the official books may be called non-official. Non-official drug compounds may be published in current journals having proven clinical value, but information about their side effects is not yet known, e.g., curcumine (sinusitis). Sources of drugs may be natural, synthetic, and biosynthetic. Drugs of plant, animal, microbiological, marine, mineral, geographical origins constitute the natural sources. The entire plant, plant parts, secretion, and exudate of plants are the sources of plant drugs. Ergot, ephedra, and datura are entire plants, *Senna* leaf and pod, leaf of *Digitalis*, bark of *Chinhona*, capsule of *Opium*, seeds of Nux vomica, rhizome of Ginger function as sources of a number of drugs useful against different diseases; kaolin, diatomite used in filtration of turbid liquids; gums, wax, gelatin, agar used as pharmaceutical auxiliaries; flavoring, sweetening agents; drugs used as vehicles or insecticides are treated in pharmacognosy as excipient. Drugs obtained from animals sources are whole animals, glandular products (thyroid organ), liver extract, polypeptide venoms, non-peptide toxins, etc. Fish liver oil, musk, beeswax, hormones, enzymes, and antitoxins sera are the products obtained from animal sources. A large number of other natural products from animal sources are used as pharmaceutic excipient and others are used as important drugs or as nutritional supplements. Many

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life-saving drugs are obtained from microbes, e.g., penicillin from *Penicillium notatum*, chloramphenicol from *Streptomyces venezuelace*, grisofulvin from *Penicillium griseofullivum*, neomycin from *Streptomyces fradiae,* and streptomycin from *Streptomyces griseus*. Aminoglycosides gentamicin and tobramycin are obtained from *Micromonospora* sp. and *Streptomyces tenebrarius*, respectively; xanthan, dextran, curdian, pullulan, emulsan, baker's yeast glycan, schizophyllan, lentinan, krestin, etc. are microbial products. Coral, sponges, fish, and marine microorganisms produce biologically potent chemicals with interesting anti-inflammatory, anti-viral, and anticancer activity, e.g., curacin A from marine cyanobacterium *Lyngbya majuscule*, eleutherobin from coral *Eleutherobia* sp., discodermolide from marine sponge *Discodermia dissoluta*, bryostatins from marine animal *Bugula neritina*, dolostatins from marine gastropod mollusk *Dolabella auricularia*, and cephalostatinsa bactericidal antibiotics from *Cephalosporium acremonium* fungus. Drugs from mineral source include both metallic and non-metallic substances like kaolin, chalk, diatomite kiesselgurh, bentonite talc, borax, and many more minerals or their salts are useful pharmacotherapeutic agents against different ailments, e.g., ferrous sulfate in iron deficiency anemia; magnesium sulfate as purgative; magnesium trisilicate, aluminum hydroxide and sodium bicarbonate as antacids; zinc oxide ointment as skin protectant, in wounds and eczema; gold salts (solganal, auranofin) as anti-inflammatory and in rheumatoid arthritis; selenium as anti-dandruff. Radioactive isotopes of iodine, phosphorus, gold, etc. are employed for the diagnosis/treatment of diseases, particularly malignant conditions. Geographical source or habitat gives information about the country or place where the drug is produced, e.g., ginger is produced in Jamaica, Nux vomica and Ispaghula in India. However, the original native place and the present geographical source may be different, e.g., Cinchona. Its native source is South America but it is now grown in Indonesia, India, and Congo. New drug compounds may be obtained from precursor molecules through microbiological conversion (e.g. atropine to tropine and tropic acid by *Corynebacterium belladonnae*), aberrant synthesis in higher plants (e.g. formation of 5-fluoronicotine from 5-fluoronictinic acid in Nicotianatabacum) as well as through culture of cells (e.g. biotransformation of β-methyldigitoxin to β-methyldigoxin, a 12β-hydroxylation by *Digitalis lanata* suspension culture, codeinone to codeine by cells of *Papaver somniferum*) and organs (e.g. tropane alkaloid-producing Solanaceae enhanced alkaloid production in roots when developed from callus culture). Potency, efficacy, and other parameters of natural drugs may be improved by a semi-synthetic process where the chemical structure is altered without any change in the nucleus, e.g., heroine, bromoscopolamine, homatropine, insulin, 6-aminopenicillanic acid derivatives. Drugs are also prepared synthetically, e.g., aspirin, oral anti-diabetics, antihistamines, amphetamine, chloroquine, chlorpromazine, general and local anesthetics; paracetamol, phenytoin, synthetic corticosteroids, sulfonamides and thiazide diuretics are synthetic products. Genetically engineered drugs include hepatitis-B vaccine, recombinant DNA engineered insulin, interferon-α-2a, and interferon-α-2b for hairy cell leukemia.

Keywords Drug sources · Pharmaceutical auxiliaries · Excipients · Official drug · Pharmacopoeia

4.1 Drugs and Crude Drugs

The word 'drug' is thought to originate from French word 'drogue-dried herbs.' There is no single and precise definition of drug, and there are different meanings in drug control law, government regulations, medicine, and colloquial usage. According to standard dictionaries definition, drug is an original, simple medicinal substance, organic or inorganic, used by itself or as an ingredient in medicine and WHO describes drugs as any substance used in a pharmaceutical product that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

A crude drug is any naturally occurring, unrefined substance derived from organic (e.g. plant, animal, bacteria, fungi, lichens, organs, whole organisms) or inorganic (e.g. minerals, rocks kaoline, bentonite) sources intended for use in the diagnosis, cure, mitigation, treatment, prevention of disease or used to otherwise enhance physical or mental well-being in humans or animals. Crude drugs are the natural therapeutic products of biological and mineral origin and have not been advanced in value or improved in condition after harvest by any process or treatment except that necessary for proper preservation and packing. Drugs may be prescribed for a limited duration, or on a regular basis for chronic disorders. Drugs are usually distinguished from endogenous biochemicals by being introduced from outside the organism. For example, insulin is called a hormone when it is synthesized by the pancreas inside the body, but if it is introduced into the body from outside, it is called a drug.

A crude drug contains pharmacologically active ingredients and requires no additional processing for use, e.g., ginseng (*Panax* spp.) root, and it may be consumed in fresh or dried condition straight in addition to grinding it into powder for use in capsules, teas, and other preparations. Some other common examples of crude drugs include the dry leaf of *Digitalis* spp., dry root of rhubarb (*Rheum rhabarbarum*), leaves and flowering tops of peppermint (*Mentha piperita*), bark of cascara (*Rhamnus purshiana*), dried milk juice of opium (*Papaver somniferum*), and whole dried insect like Spanish fly (*Lytta vesicatoria*). Traditional medicine in many cultures relies heavily on crude drugs to treat patients. Crude drugs are collected from natural sources, and some crude drugs may be cultivated to provide a controlled and readily accessible supply of the drug for use. Most can be dried or otherwise preserved to make it possible to store reserves, rather than having to rely on fresh sources of a crude drug. Doctors can prescribe a plain crude drug or prepare it to make it easier to take in the form of teas, capsules, syrups, and other pharmaceutical products. Their shelf life varies, depending on handling. Usually, they need to be kept in a cool, dark, dry place to retain potency. Traditional Chinese medicine (TCM) calls for crude drugs, as do Ayurveda, Unani, and other traditional

medical practices from cultures all over the world. The drawback of using a crude drug is an inconsistency with dosing and quality control. The potency of herbs can vary on growth condition, methods of harvesting and storage, and other factors. This necessitates expensive testing of each individual plant for dose assessment, so doctors need to estimate on the basis of the average potency.

Drugs are used for several purposes including prevention of a disease (vaccine), fight against an infection (antibiotics), temporary blocking of a normal function (general and local anesthetics), detoxification of the body (antidotes), diagnostic agents (radioisotopes), correction of dysfunction of heart, i.e., congestive heart failure (cardiotonics-digoxin), correction of hypertension (*Rauvolfia* root-reserpine), prevention of pregnancy (contraceptive), curative (eliminate the disease). Dispensing of medication is often regulated by governments into three categories: (a) over-the-counter (OTC) medications, which are available in pharmacies and supermarkets without special restrictions; (b) behind-the-counter (BTC), which are dispensed by a pharmacist without needing a doctor's prescription; and (c) prescription only medicines (POM), which must be prescribed by a licensed medical professional, usually a physician.

Official drug—any drug (crude or prepared) which is included in pharmacopoeia or in national formulary or in recognized books is called an official drug. For example, quinine, morphine, codeine, paracetamol are included in BP (British pharmacopoeia), USP (United States Pharmacopoeia), NF (National Formulary), BNF (British National Formulary), BDNF (Bangladesh National Formulary), BPC (British Pharmaceutical Codex) and so on. Unofficial drug—a drug which has been recognized earlier in the pharmacopoeia or in national formulary or in recognized books but not found in the current issue—is designated as an unofficial drug. Those substances were excluded from the recognized books due to their severe toxic effects on humans. For example, sucralfate (hyperacidity), mercurial compounds (diuretics), benzoic acid (preservative), etc. are excluded from the pharmacopoeia or other recognized literature or books due to their highly toxic effects. Non-official drug—a substance that has never been appeared in either of the official books may be called non-official. Such types of compounds may be published in current journals having proven clinical value, but we do not know about their side effects, e.g., curcumine (sinusitis).

4.2 Sources of Drugs

Before the twentieth century, drugs used for the treatment of diseases were obtained from natural sources like plants, animals, microorganisms, and minerals, and among them, plants were the major source of natural drugs. At present, most of the drugs are obtained from synthetic and biosynthetic sources. The nature was once served as the source of all medicaments and plants, especially the higher plants have been continuing the service since antiquity as important sources of novel compounds useful directly as medicinal agents, as model compounds for synthetic or

semi-synthetic structure modifications and optimization, as biochemical and/or pharmacological probes, and as sources of inspiration for generations of synthetic organic medicinal chemists. Plant-derived compounds which have recently undergone development include the anti-cancer agents, taxol and camptothecin, the Chinese antimalarial drug, artemisinin, and the East Indian Ayurvedic drug, forskolin. These and many other examples serve to illustrate the continuing value of plant-derived secondary metabolites as viable compounds for modern drug development (Newman et al. 2003; Newman and Cragg 2007). Natural sources are most primitive and abundant. Drugs obtained from the natural sources include **a**. Plant, **b**. Animal, **c**. Microbial, **d**. Marine, **e**. Mineral, and **f**. Geographical sources. Plant, Animal, Microbial and Marine may be put under common heads—the biological sources.

4.2.1 Biological Sources

Biological sources are comprised of Monera, Protista, Animalia, Plantae, and Fungi —the 5 kingdoms of Whittaker (1969).

4.2.1.1 Plant, Animal, and Microbial Sources

The entire plant, plant parts, secretion and exudate of plants are the sources of plant drugs. Ergot, ephedra, and datura are entire plants, senna leaf and pod pods, leaf of Digitalis (cardiotonic digoxin), bark of Chinhona (antimalarial quinine), capsule of Opium (analgesic morphine), seeds of Nux vomica, seeds of Eserin (anticholinestrase serine-physostigmine), rhizome of ginger function as sources of a number of drugs useful against different diseases. Though in few cases, as in lemon and orange peels and in colchicum corm, drugs are used in fresh condition, and most of the drugs are dried after collection. Crude drugs may also be obtained by simple physical processes like drying or extraction with water. Thus, the aloe is dried juice of leaves of aloe species, opium is the dried latex from poppy capsules, and black catechu is the dried aqueous extract from the wood of *Acacia catechu*. Further, drugs used by doctors or pharmacists, directly or indirectly, like cotton, silk, jute, nylon in surgical dressings or kaolin; diatomite used for filtration of turbid liquids; or gums, wax, gelatin, agar used as pharmaceutical auxiliaries or flavoring or sweetening agents or drugs used as vehicles or insecticides are treated in pharmacognosy.

Plants have always been a rich source of pharmalogical active principles (lead compounds) like alkaloids, glycosides, oils, resins, gums, tannins, and much more.

(i) Alkaloids include a vast group of chemical compounds including atropine from *Atropa belladonna*, Jimson from *Datura stramonium*, morphine from *P. somniferum*, caffeine from Coffee, Tea, Cocoa, cocaine from *Erythroxylum*

coca, digitalis from *Digitalis purpurea*, digoxin from *Digitalis lanata*, quinine from *Cinchona pubescens*, reserpine from *Rauvolfia serpentine*, tubocurarine from *Chondrodendron tomentosum*, nicotine from *Nicotina tobacum*, and muscarine from mushroom of *Inocybe* and *Clitocybe* spp.). Many of these lead compounds are useful drugs in themselves (e.g. alkaloids, morphine and quinine), and others have been the basis for synthetic drugs (e.g. local anaesthetics developed from cocaine). Psilocin, berberine, vincristine, galantamine, vincamine, quinidine, ephedrine etc. are some other alkaloids.

(ii) Terpenes and Terpenoids—Ginkgo, ginseng, valerian, *Melissa officinalis*, sage; azadirachtin, (Neem tree), artemisinin, present in *Artemisia annua* Chinese worm wood and tetrahydrocannabinol, present in *Cannabis* sp.

(iii) Glycosides—they are the combination of sugar moiety (glucone) with non-sugar moiety (aglycone). Sugar moiety is not essential for the pharmacological activity but it governs the pharmacokinetic properties of the glycoside. Pharmacological activity resides in the non-sugar aglycone moiety. Some examples are digitoxin, digoxin, and ouabain.

(iv) Cyanogenic glycosides (nitrogen-containing) include amygdalin, dhurrin, linamarin, lotaustralin, prunasin, etc.

(v) Oils—they are liquids and insoluble in water. Essential, fixed, and mineral oils are the three main categories of oils, and they are used for various medicinal purposes. Essential oils (or volatile oils)—an essential oil is a concentrated hydrophobic liquid containing volatile aroma compounds from plants and leaves no stains on evaporation. Examples of essential oils are clove oil, peppermint oil, eucalyptus oil, and ginger oil. Essential oils are subdivided into hydrocarbons (terpenes—monoterpenes, sesquiterpenes, diterpenes, etc.) and the oxygenated compounds (esters, aldehydes, ketones, alcohols, phenols, oxides, etc.). These compounds are found in the oils extracted from leaf, bud, flower parts, fruit, seed, wood, bark, and other plant parts angiosperms like anise, coriander, peppermint, rosemary, sandalwood, cinnamon, lemon, caraway, dill, clove, eucalyptus, nutmeg, camphor, and conifers like pine, fir, spruce, and juniper. Terpenes are anti-viral, anti-bacterial, anti-septic and anti-inflammatory and contain active principles like caryophyllene and valencene, chamazulene, farnesol, chamazulene, farnesene limonene, pinene camphene, cadinene, cedrene, dipentene, phellandrene, terpinene, sabinene, and myrcene. Linalyl acetate, geraniol acetate, bornyl acetate, eugenol acetate, and lavendulyl acetate are some common esters and may be found in bergamot, Clary sage, lavender, sweet marjoram, and others. Ester compounds are anti-fungal, calming and relaxing. Citral, citronellal, benzaldehyde, cinnamic aldehyde, cuminic aldehyde, and perillaldehyde are some of the examples of aldehyde compounds present in essential oils. They are found in the oils of melissa, also known as lemon balm, balm or balm mint (*Melissa officinalis*), lemongrass, lemon, mandarin, lemon-scented eucalyptus, and citronella. Aldehyde compounds of the essential oil have very distinctive anti-septic and

anti-viral activities. They can be applied topically or inhaled. Ketones include thujone, jasmine, fenchone, camphor, carvone, menthone, methyl nonyl ketone, and pinacamphone and are largely found in oils used for the upper respiratory system. They are helpful in the treatment of dry asthma, colds, flu, and dry cough. Terpenealkohols include linalool, citronellol, geraniol, farnesol, borneol, menthol, nerol, terpineol, vetiverol, benzyl alcohol, bisabolol, and cedrol. These alcohols are anti-inflammatory, anti-bacterial, anti-mycotic, and ulcer-protective and can help relieve discomfort. They may be found in rosewood, lavender, rose, lemon, eucalyptus, geranium, palmarosa, and others. Eugenol, thymo, lcarvacrol, methyl eugenol, methyl chavicolanethole, safrole, myristicin, apiol etc. are phenols present in essential oils. Phenols are responsible for the fragrance of oil and have antiseptic and anti-bacterial properties. These phenol compounds are found in clove, thyme, cinnamon, and other essential oils. Researchers believe it may possibly contain some anti-cancerous properties. Oxides of essential oil include cineol (or eucalyptol), linalol oxide, ascaridol, bisabolol oxide, and bisabolone oxide. Cineol is by far the most important member of the oxide family and is the principal constituent of eucalyptus oil. It may also be found in rosemary, cinnamon, melissa, basil, and ravensara. It is used as an anesthetic and antiseptic, and works as an expectorant.

All pure essential oils have some anti-bacterial properties. They increase the production of white blood cells, which help fight infectious illnesses. It is through these properties that aromatic herbs have been esteemed so highly throughout the ages and so widely used during the onsets of malaria, typhoid, and of course, the epidemic plagues during the sixteenth century. Research has found that people who consistently use pure essential oils have a higher level of resistance to illnesses, colds, flues, and diseases than the average person. Further indications show that such individuals, after contracting a cold, flu, or other illness, will recover 60–70% faster than those who do not use essential oils.

Fixed oils are esters of glycerin with fatty acids of high molecular weight, particularly palmitic, stearic, and oleic acids. Simple esters of glycerin are often called glycerides. The relative proportion of liquid or solid ester of glycerin due to fatty acid chain length and its degree of saturation determine the difference in consistency between oils and fats. The oils contain a greater proportion of liquid glycerides (polyunsaturated glycerin oleate), while fats are rich in solid glycerides (glycerin stearate). Fixed oils and volatile oils differ from each other in that the volatile oils contain no glycerin esters. Fixed oils may be of vegetable origin, from fruits and seeds of oil yielding plants, e.g., olive oil, mustard oil, castor oil, croton oil, peanut oil, etc. (fatty oil); coconut oil, palm oil (soft fats), or of animal origin, e.g., cod liver oil, shark liver oil, lard (hard fats), carnaiiba wax, and beeswax (harder vegetable and animal wax). Arachis, Castor, Chaulmoogra,

Coconut, Cottonseed, Linseed, Olive, Sesame, Almond also yield fixed oils. They are non-volatile and leave greasy stains on evaporation. They have caloric or food value. They form soaps with alkalies. On prolonged stay, they become rancid. They do not have marked pharmacological activity and have little pharmacological use except castor oil (purgative) or a rachis oil (demulcent). Olive oil, a monounsaturated fat, and the polyunsaturated omega-3 fats from fish and flaxseed oils are able to relieve suffering from arthritis to cancer. Vegetable fats, e.g., margarine, safflower oil, and animal fats, e.g., butter, lard are almost equally responsible for increasing blood cholesterol level and risk of heart disease and also increase the risk of cancer.

Minera oil—a mineral oil is any of various colorless, odorless, light mixtures of higher alkanes from a mineral source, particularly a distillate of petroleum. The name mineral oil by itself is imprecise and includes white oil, liquid paraffin, pariffinum liquidum, and liquid petroleum. And on the basis of their various consistencies, they are grouped as hard paraffin, soft paraffin, and liquid paraffin. Hard and soft paraffin are used as vehicles for the preparation of ointments while liquid paraffin is employed as a purgative. Baby oil is a perfumed mineral oil. Mineral oils may be used in cell culture (as an overlay covering microdrops of culture medium in petridishes during the culture of oocytes and embryos), poultry (when chickens infected with scaly mites on the shank, toes, and webs), veterinary (in vaccines as an adjuvant to stimulate a cell-mediated immune response to the vaccinating agent), and cosmetics (as common ingredient in baby lotions, cold creams, ointments, and other cosmetics).

(vi) Steroids—Terpenes with a particular ring structure. Saponins—plant steroids, often glycosylated. Phenolic compounds include curcumin, resveratrol, epigallocatechin-3-gallate, soyisoflavones.

(vii) Gums and mucilageare polysaccharide hydrocolloids of plant origin and yield mixture of sugars and uronic acids on hydrolysis. Gums are considered to be pathological products, formed by giving injury to the plant or due to unfavorable conditions (drought other stresses) by the breakdown of cell walls (extra cellular formation). Mucilages are generally normal physiological metabolites, formed within the cell (intracellular formation). Gums readily dissolve in water, whereas mucilage forms slimy masses. Natural gums can be classified according to their origin and also as uncharged or ionic polymers (polyelectrolytes). Natural gums may be obtained from seaweeds (polyelectrolytes—agar, alginic acid, sodium alginate, carrageenan, laminarin, etc.); higher plants (polyelectrolytes—gum arabic from Acacia trees, gum ghatti from Anogeissus trees, gum tragacanth from Astragalus shrubs, Karaya gum from Sterculia trees, etc.; uncharged—guar gum from guar beans, Abelmoschus gum from the fresh fruits of *Abelmoschus esculentus*, locust bean gum from the seeds of *Ceratonia siliqua*, β-glucan from oat or barley bran, chicle gum obtained from the

Chicle tree, dammar gum from the Dipterocarpaceae trees, glucomannan from Konjac plant, Mastic gum from Mastic tree, Psyllium seed husks from the Plantago plant, spruce gum from Spruce trees, tara gum from the seeds of tara tree). Natural gums may also be produced by bacterial fermentation (polyelectrolytes—gellan gum and uncharged—xanthan gum). Mucilage is obtained from the seeds of *Trigonellafoenum-graceum*.

In the food industry, they are used as thickening agents, gelling agents, emulsifying agents, and stabilizers. In other industries, they are also used as adhesives, binding agents, crystal inhibitors, clarifying agents, encapsulating agents, flocculating agents, swelling agents, foam stabilizers, etc. A large number of gums are used as pharmaceutical excipient as diluent, binder, disintegrant in tablets, thickeners in oral liquids, protective colloids in suspensions, gelling agents in gels, and bases in suppository. Gut agar and psyllium seed gums act as hydrophilic colloids and function as bulk purgatives. Gum acacia and gum tragacanth are used as suspending agents in making emulsions and mixtures. The mucilage (mannose, galactose, and xylose) obtained from fenugreek was found to be better release retardant compared to hypromellose at equivalent content. Mucilage from fresh leaves of *Hibiscus rosa-sinensis* (L-rhamnose, D-galactose, D-galacturonic acid, and D-glucuronic acid) is used for the development of sustained release tablet has been reported. Aloe mucilage from the leaves of *Aloe barbadensis* contains arabinan, arabinorhamnogalactan, galactan, galactogalacturan, glucogalactomannan, galactoglucoarabinomannan, glucuronic acid, etc. A controlled delivery system of glibenclamide using aloe mucilage proved that Aloe mucilage can be used as a matrix forming material for making controlled release glibenclamide matrix tablets.

(viii) Resin in is a polymer hydrocarbon secretion of many plants, particularly coniferous trees. It is distinct from cell sap, latex, gum, or mucilage. They are produced by oxidation and polymerization of volatile oils. Natural resins are typically fusible and flammable organic substances that are transparent or translucent and are yellowish to brown in color; insoluble in water but soluble in alcohol, chloroform, and ether. Asafoetida, Benzoin, Colophony, Copaiba, Guaiacum, Guggal, Mastic, Myrrh, Peru Balsam, Sandarac, Storax, Tolu Balsam, Tar, Coal Tar oleoresins (aspidium); gum resins (asafoetida); oleogum resin (myrrh); balsams (benzoin, tolu, peru); benzoin shellac, podophyllum, etc. are some of the common examples of resin. They may combine with oil, mucilage, and gum. Benzoin is used as inhalation in common cold, tincture benzoin is applied as antiseptic protective sealing over bruises, colophony (an oleoresin) is used as an ingredient in various plasters, shellac (from *Lucifer lacca*) is used for enteric coating of tablets, balsams are used in the treatment of cough and bronchitis for their antiseptic and protective properties, and podophyllum is used as an irritant purgative.

(ix) Tannins are astringent, bitter, non-nitrogenous, polyphenolic plant constituents. Tannin binds to and precipitates proteins and various other organic

compounds including amino acids and alkaloids. Tannins are common in fruits (grapes, persimmon, blueberry, etc.), in tea, in chocolate, in legume forages (trefoil, etc.), in legume trees (*Acacia* spp., *Sesbania* spp., etc.), in grasses (sorghum, corn, etc.). Other important tannin-containing plants are *Quercus* sp. (oak), *Acer* sp. (maple), *Betula*sp. (birch), *Salix caprea* (willow), *Pinus* sp. (Pine), *Sorghum* sp. Pyrogallol tannins are glycosides of glucose that occur in oak galls. Pyrocatechol tannins are sugar-free derivatives of catechol that are present in catechu and eucalyptus. Tannic acid is tannin that is obtained from oak galls and is used for treating burns and diarrhea.

(x) Toxins-Botulinum toxin from *Clostridium botulinum* prevent cholinergic transmission and could well prove a lead for the development of novel anticholinergic drugs.

Animal sources

Drugs obtained from animals sources are (i) whole animals, (ii) their organs, and (iii) glandular products (thyroid organ) and extract (liver), etc. Whole animals include European medicinal leech *Hirudo medicinalis*, Mexican medical leech *Hirudo manillensis* (hirudin, heparin), cantharides-skin irritants (form *Mylabris* sp and *L. vesicatoria*-Spanish fly, the blistering beetles of Coleoptera), lac or shellac (the resinous substance prepared from a secretion of the insect-lac bug, *Lacciferlacca*), musk scent (the dried secretion from the preputial follicles of the musk deer, *Moschusmoschiferus*), civet (the secretion obtained from the perineal follicles of civet cats, *Viverra* spp.), chalk (finely powdered whitish or grayish rock), which consists mainly of the shells of unicellular microorganisms, *Foraminifera* (amoeboid protists) and coccolithophores;

(ii) different organs and their products include skin of the African clawed frog *Xenopuslaevis* (antibiotic peptides), skin extracts of the Ecuadorian poison frog *Ameeregabilinguis* (potent analgesic compound epibatidine), pancreas of cow and pork (insulin, hormone), cow stomach (pepsin), thyroid gland (thyroxin), liver (liver extract, vit. B_{12}), cod liver oil (from *Gadus* spp., mainly from the Atlantic cod *Gadus morhua*), pregnant woman (human chorionic gonadotropin-HCG hormone), post menopausal woman urine (menotrphin), human kidney cells (urokinase), antitoxic sera, etc. are some of the animal sources for many valuable drugs as well as halibut-liver oil (from *Hippoglossus vulgaris*), suet (hard raw beef or mutton fat), lard (pig fat), spermaceti (wax found in the head cavities of the sperm whale), wool fat (waxy substance, skin lipid, secreted by the sheep *Ovis aries*); and

(iii) their products and extracts include venoms and toxins from snakes, spiders, scorpions, insects, etc. are polypeptides (α-bungarotoxin from cobras) or non-peptide toxins (tetrodotoxin from the puffer fish). They have been used as lead compounds in the development of novel drugs, e.g., teprotide, a peptide from the Brazilian viper, was the lead compound for the development of the antihypertensive agents cilazapril and captopril. Gelatin (obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue and bones of animals like cow hide splits, bones, pork skin, and fish skin), honey (produced bees *Apis* spp.), beeswax (natural wax produced in the bee hive of honey by *Apis* spp.), chitin (most

abundant natural amino polysaccharide, next to cellulose, derived from two marine crustaceans, shrimp—*Penaeus kerathurus* and crabs—*Carcinus mediterraneus* shells), chitosan—deacetylated chitin derivative, chondroitin sulfate (a sulfated glycosaminoglycan and an important structural component of cartilage and provides much of its resistance to compression, manufactured from cow cartilage), hyaluronic acid (non-sulfated glycosaminoglycan distributed throughout connective, epithelial, and neural tissues), animal (derived from cows, pigs pancreases and until the 1980s, animal insulin was the only treatment for insulin dependent diabetes), human chorionic gonadotropin—hCG (a hormone produced by the syncytiotrophoblast of the placenta following pregnancy of a woman), thyroxin (from sheep thyroid), pituitary gonadotropins (glycoprotein hormones secreted by gonadotropic cells of the anterior pituitary, used in fertility medication), heparin (an anticoagulant), vaccines (live attenuated viruses—rubella, measles, oral polio, mumps; or bacteria—bacillus calmette-guerin, BCG; inactivated viruses—parenteral polio, hepatitis A; or parts of the virus—pneumococcal vaccine, influenza; inactivated bacterial toxins—diphtheria and tetanus; genetically engineered—hepatitis B vaccine by inserting a segment of the viral gene in a yeast cell); sera (antidiphtheria, antitetanus sera from horse and sheep); etc.

Microbial sources

Many life-saving drugs are obtained from microbes such as penicillin from *Penicillium notatum*, chloramphenicol from *Streptomyces venezuelace*, anti-fungal drug grisofulvin from *Penicillium griseofullivum*, neomycin from *Streptomyces fradiae* and streptomycin from actinobacterium *Streptomyces griseus*. Aminoglycosides such as gentamicin and tobramycin are obtained from *Micromonospora* sp. and *Streptomyces tenebrarius*, respectively; xanthan (polysaccharide gum secreted by *Xanthomonas campestris*, composed of repeat units of glucose, mannose, and glucuronic acid in the molar ratio 2:2:1), dextran (polysaccharide of glucose synthesized by lactic acid bacteria *Leuconostoc mesenteroides, Streptococcus mutans, Lactobacillus brevis*), curdian (β-1,3-glucan polymer, product of *Agrobacterium biobar* and *Alcaligenes faecalis*), pullulan (a polysaccharide polymer of maltotriose units produced from starch by the fungus *Aureobasidium pullulans*), emulsan (a polyanionic heteropolysaccharide bioemulsifier produced by *Acinetobacter calcoaceticus* RAG-1.), baker's yeast glycan (polysaccharide derived from ruptured yeast cell walls of *Saccharomyces cerevisiae*), schizophyllan (a neutral extracellular polysaccharide produced by the fungus *Schizophyllum commune*), lentinanan (intravenous anti-tumor polysaccharide isolated from the fruit body of an edible mushroom shiitake—*Lentinula edodes*), krestin, or polysaccharide-K—PSK (a protein-bound polysaccharide, an anti-cancer immunologic adjuvant, from the mushroom fruitbody of *Trametes versicolor*), and scleroglucana (water-soluble polysaccharide produced by fermentation of the filamentous fungus *Sclerotium rolfsii*). Microbial metabolites other than antibiotic are also known, e.g., asperlicin (a novel antagonist of a peptide hormone, cholecystokinin—CCK) from *Aspergillus alliaceus*, lovastatin from oyster mushrooms—*Pleurotus ostreatus* and Chinese red yeast rice—*Monascus purpureus*.

4.2.1.2 Marine Sources

Coral, sponges, fish, and marine microorganisms have a wealth of biologically potent chemicals with interesting inflammatory, anti-viral, and anticancer activity. For example, curacin A, lipid constituent, from a marine cyanobacterium *Lyngbya majuscule* shows potent anti-tumor activity. Other anti-tumor agents derived from marine sources include eleutherobin from coral *Eleutherobia* sp., discodermolide from the Caribbean marine sponge *Discodermia dissoluta*, bryostatins from colonial marine animal of North Carolina *Bugula neritina*, dolostatins from small marine gastropod mollusk *Dolabella auricularia*, and cephalostatinsa, a broad class of bactericidal antibiotics from *Cephalosporium acremonium* fungus.

4.2.2 Mineral (Metallic and Non-metallic) Sources

Drugs from mineral source are kaolin, chalk, diatomite and many more. Minerals or their salts are useful pharmacotherapeutic agents. For example, ferrous sulfate ($FeSO_4$) is used in iron deficiency anemia, magnesium sulfate ($MgSO_4$) is employed as purgative, magnesium trisilicate, aluminium hydroxide $\{Al(OH)_3\}$ and sodium bicarbonate ($NaHCO_3$) are used as antacids for hyperacidity and peptic ulcer, zinc oxide ointment as sunscreen, skin protectant, in wounds and in eczema, gold salts (solganal, auranofin) as anti-inflammatory and in rheumatoid arthritis, bentonite (absorbent aluminium phyllosilicate clay), talc (hydrated magnesium silicate). Kaolin (aluminium silicate) is used as an adsorbent in antidiarrheal mixtures, mercurial salts are used in syphilis andiodine is used as antiseptic. Borax and fluorine have antiseptic properties, selenium as selenium sulfide is used in anti-dandruff shampoos and petroleum is used in the preparation of liquid paraffin. Radioactive isotopes of iodine, phosphorus, gold are employed for the diagnosis/treatment of diseases particularly malignant conditions. Kiesselguhr, the fossilized remains of diatoms, is a form of silica composed of the siliceous shells of diatoms.

4.2.3 Geographical or Habitat Sources

Geographical source or habitat gives us information about the country or place where the drug is produced. *Zingiber officinale* is indigenous to southern China and was spread eventually to the Spice Islands (Maluku province of Indonesian), other parts of Asia and subsequently to West Africa and the Caribbean and *Cannabis indica, Tamarinds indica*, *Strychnosnux-vomica* and *Plantago ispaghula* in the Indian subcontinent. In some cases, the original native place of a drug is not the same as the present geographical source, e.g., cinchona is a native of South America and is at present cultivated in Indonesia, India, and Congo.

4.2.4 New Drug from Microbiological Conversion, Aberrant Synthesis in Higher Plants, Cell Tissue, and Organ Culture

Microbial conversion

Microbial conversion or transformation is an important manufacturing tool in chemical and pharmaceutical industries. It is responsible for minor structural modifications in exogenous substances (non-nutrient substances) by enzyme systems that lead to the formation of molecules with relatively greater polarity. Microbial transformation of natural products into active drug substances is a highly active area in green chemistry. Biotransformation of natural products into less toxic derivatives (anti-tumor agents), fractionation of racemic mixtures, etc. are some of the major objectives of microbial transformation. Microbes with the aid of the biocatalysts they produce can simplify or enable the production process of complex chemicals and drug intermediates, can add stereo specificity to the process and thus can eliminate the need for complicated separation and purification steps. Biocatalysts selectively produce useful products under relatively mild conditions compared to chemical catalysts. The basic chemistry reactions (lengthy and more tedious) include stereo selective hydroxylation, epoxidation, and oxidation reactions or addition, elimination, substitution, pericyclic, rearrangement and redox reactions, the remarkable features of biotransformation reactions is the maintenance of the original carbon skeleton after obtaining the products. Microorganisms have great potential for inducing many alternatives of innovative and aturaimprovised enzyme systems which are capable for converting terpenes, steroids, alkaloids including artemisinin, taxol, panaxosides or ginsenosides, bufalin, diosgenin, opiate alkaloids, and other natural products (Hegazy et al. 2015). Microorganisms are capable of producing unique enzymes which are stable toward heat, alkali and acids (Hotta et al. 2002; Gershwin 2006). Biotransformation reactions may involve various events such as the formation of stable intermediates (with or without toxic or pharmacologic activity), short-lived reactants may be generated, or biotransformation reactions can result in chemically stable compounds with desired pharmacological activity.

The use of microbial transformation is named White Biotechnology, an emerging field of modern biotechnology that serves industry. Some of the examples of microbial transformation of bioactive natural products are transformation of artemisinin derived from *Artemisia annua* by *Streptomyces* sp. (Liu et al. 2006) as well as by *Cunninghamella echinulata* and *Aspergillus niger* (Zhan et al. 2002); taxol and its analogues isolated from the bark of *Taxus brevifolia* by *Streptomyces* sp. (Chen et al. 2001); transformation of panaxosides (ginsenosides) isolated from the roots of *Panax ginseng* (Bae et al. 2002; Hasegawa et al. 2002; Liu et al. 2004); transformation of opiate alkaloid—evodiamine of Evodia rutaecarpa by *Penicillium*

janthinellum (Madyastha and Sridhar 1998; Li et al. 2006); transformation of bufalin by *Alternaria alternate* (Ye et al. 2005) and *Pseudomonas aeruginosa* (Zhan et al. 2003).

Aberrant synthesis in higher plants

Higher plants produce some unnatural compounds as result of feeding transformable precursors. These unnatural compounds or aberrant compounds are analogues of naturally existing compounds, and higher plants can synthesize (aberrant synthesis) such compounds (aberrant compounds) when they are fed with closely related (in structure) natural intermediates. Transformation of DL-*p*-flurophenyl [3-^{14}C]alanine to unnatural 4′-fluoro[2-^{14}C]chrysin by *Scutellaria galericulata* which normally contains the 7-glucouronide of chrysin, *Nicotiana tabacum* feeding with 5-fluoronicotinic acid produced 5-fluoronicotine, formation of (–)-N-methylanabasine from N-methyl-Δ^1-piperideinium chloride in *Nicotiana tabacum* and *N. glauca*, transformation of unnatural codeine derivatives to unnatural morphine derivatives in *P. somniferum*, transformation of unnatural precursor 4(5)-Aminomethylimidazole to aberrant metabolite 4(5)-[N-Isovalerylaminomethyl]-imidazole in *Dolichothele sphaerica* are some examples of aberrant synthesis of unnatural molecules in higher plants. This sector is not yet commercially exploitable like cell tissue and organ culture of higher plants for biotransformation.

Plant cell tissue and organ culture

Plant cell tissue and organ culture constitute a sustainable, controllable, and nature-independent tool for the industrial production of plant most high-value natural products (NPs). About 200,000 NPs have been identified so far (Fiehn 2002), and some of these have been utilized as drugs (codeine, morphine, paclitaxel) (Newman and Cragg 2012), food-flavoring and coloring agents (saffron, spearmint, and anthocyanins) (Delgado-Vargas et al. 2000; Ambati et al. 2014), pest and disease management chemicals (nicotine, strychnine, and azadirachtin) (Copping 1998; Miresmailli and Isman 2014) and cosmetics and fragrance products (lavender, rosemary, and aloe vera) (Cavanagh and Wilkinson 2002; Javed 2014).

Many of the high-value NPs source plants grow wild with slow growth, low concentration of the active molecules in the source plant, complex molecular structure with multiple chiral centers, and region-specific as well as stereo-specific properties linked to function of the NP molecules made total chemical synthesis difficult or unprofitable. The production of NPs via semi-synthesis represents an alternative approach that can circumvent some of the issues associated with the total synthesis of these high-value plant chemicals, e.g., the production of the diterpenoid, paclitaxel (Howat et al. 2014). Semi-synthetic route requires abundant chemical precursor integral to the biosynthetic pathway, and the route is costly and often also generates toxic by-products (Wu and Chappell 2008).

Biotransformation in plant cells or organ tissues is another method that can be used to produce high-value-chemical products (Talano et al. 2012; Murthy et al. 2014). Biotransformation is an important alternative to the semi-synthesis strategy

and enables improved stereo-specific characteristics, bioavailabilty and the potential to lower the toxicity of the desired NPs. Biotransformation involves the chemical conversion based on exploiting different enzyme reactions (e.g. hydroxylations, glycosylations, oxidoreduction, hydrogenation, hydrolysis, methylations, acetylation, isomerizations, esterifications) of supplied substances biological systems, plant cells organ tissues (Giri et al. 2001; Ishihara et al. 2003; Banerjee et al. 2012). This method is inexpensive and available, and plentiful products can be transformed into rare, expensive, and high-value NPs. With the advancement of 'omics' technologies, biotransformation of natural compounds through hairy root cultures has become easier than before (Banerjee et al. 2012). For example, biotransformation of cinnamyl alcohol to rosavins in hairy roots of *Rhodiola kirilowii* produced 80–95% of the glycosides released to the culture media (Grech et al. 2014). Biotransformation may also lead to the discovery of novel plant NPs, e.g., a novel terpenoid indole alkaloid, identified as 3-hydroxy-4-imino-catharanthine, in suspension cultures of *Catharanthus roseus* was the product of biotransformation of catharantine (He et al. 2015).

4.2.5 Semi-synthetic, Synthetic, and Biosynthetic Sources

Semi-synthetic sources

In semi-synthetic drugs, the nucleus of drug obtained from natural source is retained but the chemical structure is altered. Sometimes semi-synthetic processes are used to prepare drugs when the natural sources may yield impure compounds or when the synthesis of drugs (complex molecules) may be difficult, expensive, and commercially unviable. Some examples are semi-synthetic human insulin and 6-aminopenicillanic acid derivatives. Prepared by chemically modifying substances that are available from natural source to improve its potency, efficacy and also reduce side effects. Semisynthetic drugs from plant sources include heroine from morphine, bromoscopolamine from scopolamine, homoatropine from atropine, and from animal sources are animal insulin changed to be like human insulin and 6-aminopenicillanic acid derivatives. Other examples include apomorphine, diacetyl morphine, ethinyl estradiol, homatropine, ampicillin and methyl testosterone.

Synthetic sources

In semi-synthetic drugs, the nucleus of the drug from natural source as well as its chemical structure is altered. At present, majority of drugs used in clinical practice are prepared synthetically, such as aspirin, oral antidiabetics, antihistamines, amphetamine, chloroquine, chlorpromazine, general and local anesthetics, paracetamol, phenytoin, synthetic corticosteroids, sulphonamides, and thiazidediuretics. Most of the synthetic drugs are prepared synthetically, i.e., by chemical process (reaction) with the help of the knowledge of phytochemical investigation.

Advantages of synthetic drugs include their chemical purity, simple and cost-effective method of preparation and high quality. Since the pharmacological activity of a drug depends on its chemical structure and physical properties, more effective and safer drugs can be prepared by modifying the chemical structure of the prototype drug.

Biosynthetic sources (genetically engineered drugs)

This is relatively a new field which is being developed by mixing discoveries from molecular biology, recombinant DNA technology, DNA alteration, gene splicing, immunology, and immune pharmacology. Some of the recent developments are genetically engineered novel vaccines (Recombivax HB—a hepatitis-B vaccine), recombinant DNA engineered insulin (Humulin–human insulin) for diabetes and interferon-alpha-2a and interferon-alpha-2b for hairy cell leukemia. Recombinant DNA technology involves cleavage of DNA by enzyme restriction endonucleases. The desired gene is coupled to rapidly replicating DNA (viral, bacterial, or plasmid). The new genetic combination is inserted into the bacterial cultures which allow production of vast amount of genetic material. In this process, huge amount of drugs can be produced, drug can be obtained in pure form, and it is less antigenic. Well-equipped laboratory and highly trained staffs are required, and moreover, it is a complex and complicated technique.

4.2.6 Importance of Crude Drugs from Natural Sources

The natural drugs and their active constituents play important roles as easily available and cost-effective medicaments to rural people as well as in the development of modern medicine as a source of diversified bioactive compounds for direct use or as lead compounds. Natural sources (plants, animals, marine organisms, ants, frogs, worms, microbes, etc.) comprise a very rich store for new bioactive compounds such as atropin, marine anti-viral acyclovir, antiprotozoal apicidin, ephedrine, morphine, caffeine, salicylic acid, digoxin, taxol, galantamine, vinblastine, vincristine, colchicine, quinine, artemisinin, etoposide, teniposide, paclitaxel, camptothecin derivatives topotecan and irinotecan, marine anticancer drug trabectidin, etc. useful for the development of modern drugs and natural compounds could be good models for developing novel drug molecules (Sagar et al. 2010; von Bargen et al. 2013). Natural sources are continually providing diverse groups of unique bioactive lead compounds for new drug discovery and development.

The bioactive compounds digoxin and digitoxin as well as vinblastin and vincristin are the products of Digitalis and Catharanthus plants, respectively, and are now used effectively in modern medicine against heart diseases and cancer treatment. Yew tree (*Taxus baccata, T. brevifolia*) is an another example of the life-saving qualities of plants contains precious taxane diterpenes, convertible into

the chemotherapy drug taxotere (docetaxel), taxol (paclitaxel), etc. are widely used as chemotherapy agents. Cabazitaxel is FDA approved to treat hormone-refractory prostate cancer. Both taxanes (disrupt microtubule function) and vinca alkaloids (prevent mitotic spindle formation) are, therefore, named spindle poisons or mitosis poisons, but they act in different ways. Taxanes are difficult to synthesize because of their numerous chiral centers (taxol contains 11 chiral centers). The presence of taxanes in the shells and leaves of *Corylus avellana* (the common hazel plant) has been reported several investigators (Ottaggio et al. 2008; Hoffman and Shahidi 2009). Baccatin III isolated from *Taxus baccata* (Yew tree), which is modified into taxol, a potent anticancer drug. Elicitation due to ultrasound (US) and salicylic acid (SA) individually as well as synergistically enhanced taxol production by hazelnut cells in culture (Rezaei et al. 2011).

A few natural sources provide a number of very useful drugs which are difficult to produce commercially and economically by synthetic or chemical and microbiological means, e.g., digoxin and digitoxin as well as vinblastin and vincristin. Wild source or cultivation would be the way to produce these drugs. Bioactive compounds after partial modification (synthetic) may be developed into compounds of modern medicine, e.g., preparation of steroid hormones from diosgenin by acetolysis and oxidation and further preparation of cortisone by microbial conversion. Besides, natural products would serve as a model (lead compound) for the synthesis of new drugs, e.g., morphine is the model of a large group of potent drugs, cocaine for local anaesthetics, atropine for certain spasmolytics. Morphine is a strong analgesic (and also narcotic) while its structural modified form codeine is moderately analgesic (and less narcotic). Natural compounds may serve as lead compounds (prototype) for synthetic drugs with pharmacological activities similar to original compounds, e.g., salicin (alcoholic glycoside from Salix stem bark used as anti-rheumatism to headache, diaphoretic, and anti-malaria) on oxidation produces salicylic acid and then aspirin. Digitonin (saponin glycoside), otherwise a fish poison, shows little or therapeutic activity, but after some structural changes by chemical or microbiological treatments is converted into potent drugs of therapeutic importance, especially the testerone, progesterone, cortisone which are useful for curing some diseases.

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Chapter 5
Classification of Drugs, Nutraceuticals, Functional Food, and Cosmeceuticals; Proteins, Peptides, and Enzymes as Drugs

Abstract A crude drug is a naturally occurring unrefined substance consisting of whole plant or herb, any part of it, exudate or extract of it. Crude drugs of different sources are arranged (i) in alphabetical order of their Latin (e.g., European pharmacopoeia) and English (e.g., USP and BPC) names, common names, or sometimes local language names (e.g., Acacia, Benzoin, Cinchona, Dill, Ergot, Fennel); (ii) according to structural characteristics as organized (e.g., part or organ of the plant and animal such as leaves, stems, roots, rhizome, barks, flowers, seeds, hair, fibers) and unorganized drugs (e.g., acellular products of plant and animal such as gum, latex, juice, oil); (iii) following the principles of natural relationship and evolutionary development of plants or animals taxa in Phyla, Orders, Families, Genera, Species, Sub-species, etc.; (iv) according to their pharmacological action or therapeutic uses (e.g., bulk purgatives, emollient purgatives; digitalis, squill, and strophanthus cardiotonics), (v) on the basis of the chemical nature of important constituent or their biosynthetic pathways (e.g., alkaloids, glycosides), (vi) on the chemical similarity of a taxon or certain classes of plants (e.g., tropane alkaloids as a chemotaxonomic marker of Solanaceae members; berberine alkaloid in Berberis and Argemone; rutin in Rutaceae members; ranunculaceous alkaloids in Ranunculaceae) in (i) alphabetic, (ii) morphological, (iii) taxonomical, and (iv) pharmacological or therapeutic (v) in chemical (vi) in chemotaxonomic systems of classifications. The classification of allopathic drugs is based on the clinical usage may be grouped into non-prescription drugs or over-the-counter drugs and prescription drugs. The anatomical therapeutic chemical (ATC) classification of modern drugs is a more elaborate one that categorizes drugs into 14 main classes according to the organ or biological system on which they act as well as their therapeutic, pharmacological, and chemical properties. On the basis of properties and uses, allopathic drugs are also classified as antibiotics, antacids, antigas medicines, wormicides, steroid medicines, medicines for the external uses, antiallergens and antihistamines, antihypertensive, antidiabetic, antidiarrheal medicines, laxatives, medicines for anticold and cough, antiepileptic, antispasmodic, antipyretics, analgesics, antivomiting, antiulcer, hematinic, tranquillizers, medicines for giddiness, enzymes, vitamins, mineral compounds, amino acids, etc. Nutraceuticals are medicinal foods, nutritional supplements, dietary supplements, or

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food components made from herbal or botanical raw materials that can deliver health benefits beyond basic nutrition, modulate immunity, and/or prevent and cure specific diseases and increase life expectancy. They cover a wide spectrum of substances ranging from natural diets, herbal products, biofortified crops, genetically modified and processed food products. Nutraceuticals are classified as traditional or natural nutraceuticals (e.g., nutrients, herbals, phytochemicals, probiotic microorganisms, nutraceutical enzymes) and non-traditional or artificial nutraceuticals (e.g., fortified and recombinant nutraceuticals). Cosmeceutical is a hybrid combination of cosmetics and pharmaceuticals containing biologically active ingredients to add medical or drug-like benefits (e.g., cream, lotion, ointment and similar other substances containing botanical and marine extracts like vitamins, peptides). These products are intended for the improvement of health and beauty of the skin and hair. They contain a wide spectrum of biologically active ingredient of natural origin including moisturizer, vitamin, sun protector, skin whitener, free radical scavenger, etc. Cosmeceuticals are classified on the basis of (a) use: (i) skin cosmeceutical products, (ii) hair cosmeceutical products, and (iii) others; (b) active ingredient content and function as (i) retinoids, (ii) sunscreens, (iii) moisturizers, (v) depigmenting agents, (vi) exfoliants, (vii) antioxidants, (viii) proteins/peptides, and (ix) growth factors.

Keywords Classes of drugs · Nutraceuticals · Cosmeceuticals · Biofortified foods

5.1 Classification of Crude Drugs

Higher plants, microbes, animals, and minerals are the main natural sources of crude drugs. Enzymes and antibiotics used in modern medicine are also obtained from natural biological sources. Classification is a means of the systematic arrangement of large varieties or quantities of things into smaller groups on the basis of some similar characters present in them. A method of classification should be simple, easy to use, and free from confusion and ambiguities. In order to conveniently study crude drugs of different origin, it is necessary to classify them into some smaller groups by using certain criteria, i.e., according to morphological, taxonomical, chemical, and pharmacological characters. Morphological classification is more helpful to identify and detect adulteration; for studying evolutionary developments, the drugs are classified according to taxonomical classification, the activity of a drug is due to its chemical constituents, and therefore, the drugs are divided according to the presence of chemical components and pharmacological classification of drugs is more relevant to study therapeutic utility of the drugs. However, each of these systems has its own merits and demerits.

5.1.1 Alphabetical Classification

Alphabetical classification is the simplest way of classification of any disconnected items. Crude drugs are arranged in alphabetical order of their Latin and English names (common names) or sometimes local language names (vernacular names). Some of the examples are as follows: Acacia, Benzoin, Cinchona, Dill, Ergot, Fennel, Gentian, Hyoscyamus, Ipecacuanha, Jalap, Kurchi, Liquorice, Mints, Nux-vomica, Opium, Podophyllum, Quassia, Rauwolfia, Senna, Vasaka, Wool fat, Yellow bees wax, Zeodary. In European pharmacopoeia, these are arranged according to their names in Latin, where in USP and BPC, these are arranged in English.

Some of the pharmacopoeias, dictionaries, and reference books, which classify crude drugs according to this system, are as follows:

i. Indian pharmacopoeia;
ii. British pharmacopoeia;
iii. British Herbal pharmacopoeia;
iv. US pharmacopoeia and National Formulary;
v. British Pharmaceutical Codex;
vi. European pharmacopoeia;
vii. Bangladesh pharmacopoeia; and
viii. International pharmacopoeia.

In addition, a number of the more enlightened nations have pharmacopoeias, so there are the German pharmacopoeia, the Swiss, the Japanese, etc. The pharmacopoeia (literally, 'drug-making') is a book which defines and standardizes certain drugs and their preparations. It is a reference work for pharmaceutical drug specifications. Its aim is to establish definiteness for a selected number of those in extensive use by physicians. The pharmacopoeia's drugs and preparations are considered as official and protected by one or more National Acts related to Food and Drugs Policies. The official preparations are, therefore, the ones that are standardized; hence, they are the preparations that can be obtained of uniform strength throughout the country, and they are, for the most part, the forms in which remedies can be readily supplied by the pharmacist. Hence, the official preparations are the forms to be preferred by the physician.

The International pharmacopoeia (Ph. Int.) is published by the WHO with the aim to achieve a wide global harmonization of quality specifications for selected pharmaceutical products, excipients, and dosage forms. The activities related to Int. Ph. are an essential element in overall quality control and assurance of pharmaceuticals contributing to the safety and efficacy of medicines. The work of the International pharmacopoeia is carried out in collaboration with members of the WHO Expert Advisory Panel on the International pharmacopoeia and Pharmaceutical Preparations and with other specialists.

Merits

i. It is easy and quick to use;
ii. There is no repetition of entries and is devoid of confusion; and
iii. In this system location, tracing and addition of drug entries are easy.

Demerits

i. There is no relationship between previous and successive drug entries.

5.1.2 Morphological Classification

Under morphological classification, the drugs are arranged according to the part or organ of the plant and animal used such as leaves, stems, roots, rhizome, barks, flowers, seeds, hair, and fibers (organized drugs) and plant product such as gum, latex, juice, and oil (unorganized drugs). The organized drugs are obtained from the direct parts of the plants or animals and containing cellular tissues, whereas the unorganized drugs are prepared from plants or animals by some intermediate physical processes such as incision, drying, or extraction with a solvent and do not contain any cellular tissues.

According to this system, crude drugs are broadly divided into the following two main groups on the basis of their apparent morphological forms of occurrence and structural organization of the plant or animal parts and their natural products:

i. **Organized drugs**: The drugs obtained from the direct parts of the plants and animals and containing cellular tissues are known as organized drugs, e.g., rhizomes, barks, leaves, fruits, entire plants, hair, and fibers.
ii. **Unorganized drugs**: The drugs which are prepared from plants or animals by some intermediate physical processes such as incision, drying, or extraction with a solvent and not containing any cellular plant or animal tissues are called as unorganized drugs. Aloe juice, opium latex, agar, gambir, gelatin, tragacanth, benzoin, honey, beeswax, lemon grass oil, etc., are examples of unorganized drugs.

Differences between organized and unorganized drugs are shown below in tabular form (Table 5.1).

The organized crude plant drugs are further divided into the following two groups according to the position of the plant organs that constitute the crude drugs:

i. **Drugs from over ground organs**: These include all drugs that are derived from the overground or aerial parts or organs of plants.
ii. **Drugs from underground organs**: These include all drugs that are derived from underground or subterranean parts or organs of plants.

Table 5.1 Differences between organized and unorganized drugs

Organized drugs	Unorganized drugs
(i) These may be of plant or animal origin	(i) These may be of plant, animal, or mineral origin
(ii) These are direct part of plant or animal	(ii) These are the product of plant, animal, or mineral
(iii) These have cellular structure	(iii) These do not have well-defined cellular structure
(iv) Generally identified by morphological character	(iv) Generally identified by organoleptic properties
(v) Examples: digitalis leaf, cinchona bark, ephedra stem, etc.	(v) Examples: Agar, gelatin, honey, etc.

The crude drugs of the over ground organs are again divided into herb, leaf, flower, fruit, seed, bark, and wood drugs and those of the underground organs into root, rhizome, bulb, and corm drugs on the basis of their morphological identity. The unorganized crude drugs are also similarly divided into smaller groups on the basis of the nature of the natural product, such as juices, lattices, extracts, gums, resins and balsams, fats, oils, and waxes.

Classification of drugs on the basis of morphological characters with example is given in Table 5.2.

Merits

i. Morphological classification is more helpful to identify and detect adulteration.
ii. This system of classification is more convenient for practical study, especially when the chemical nature of the drug is not clearly understood.

Demerits

i. The main drawback of morphological classification is that there is no correlation of chemical constituents with the therapeutic actions.
ii. Repetition of drugs or plants occurs.

5.1.3 Taxonomical Classification

Taxonomical classification is purely a botanical classification and is based on the principles of natural relationship and evolutionary developments. The drugs are classified according to plants or animals from which they are obtained into Phyla, Orders, Families, Genera, Species, Sub-species, etc. (Table 5.3).

As all the entire plants are not used as drugs, part of the plant is used as a drug, for example, cinnamon bark, and thus, it is of no significance from an identification point of view to put plants in a taxonomic order. Table 5.4 gives the account of

Table 5.2 Classification of drugs on the basis of morphological characters with example

Classification of drugs	Drug examples
1. Organized drugs	
(i) Wood	Quassia, Sandal wood, Red Sandal wood
(ii) Leaves	Digitalis, Eucalyptus, Gurniar, Pudina, Senna, Spearmint. Squill, Tulsi, Vasaka, Coca, Buchu, Hamamelis, Hyoscyamus, Belladonna, Tea
(iii) Barks	Arjuna, Ashoka, Cascara, Cassia, Cinchona, Cinnamon. Kurchi, Quillaia, Wild Cherry
(iv) Flowering parts	Clove, Pyrethrum, Saffron, Santonica, Chamomile, Artemisia
(v) Fruits	Amla, Anise, Bahera, Bitter orange peel, Capsicum, Caraway, Cardamom, Cassia, Colocynth. Coriander, Cumin, Dill, Fennel, Gokhru, Hirda, Lemon peel, Psoralea, Senna pod, Star anise, Tamarind, Vidang, Bael
(vi) Seeds	Bitter almond, Black mustard, White mustard, Cardamom, Colchicum, Linseed, Neem, Nutmeg, Nux vomica, Physostigma, Psyllium, Strophanthus, Isabgol, Castor
(vii) Roots, rhizomes and bulb	Aconite, Ashwagandha, Calamus, Calumbs, Colchicum conn, Dioscorea, Calanga, Garlic, Gentian, Ginger, Ginseng, Glycyrrhiza, Podophyllum, Ipecac, Iponnea, Jalap, Jatamansi, Male fern, Picrorhiza, Piplam, Rauwolfia
(viii) Plants and herbs	Rhubarb, Saussurea, Senega, Shatavari, Turmeric, Valerian, Squill, Serpentary, Indian Podophyllum, Krameria, Derris, Indian Valerian, Andrographis, Bacopa, Banafsha, Belladonna, Cannabis, Centella, Chirata, Chondrus, Datura, Ephedra, Ergot, Hyoscyamus. Kalmegh, Lobelia, Punarnava, Shankhpushpi, Stramonium, Vinca, Yeast, Cantharides
(ix) Hair and fiber	Cotton. Hemp, Jute, Silk, Flax
2. Unorganized drugs	
(i) Dried latex	Opium, Papain, Gutta-percha
(ii) Dried juice	Aloe, Kino, Red gum
(iii) Dried extracts	Agar, Alginate, Black Catechu, Pale Catechu, Pectin, Gelatin, Curare
(iv) Gums	Acacia, Guar gum, Indian gum, Sterculia, Tragacanth, Ghatti gum
(v) Resins	Asafoetida, Benzoin, Colophony, Copaiba, Guaiacum, Guggal, Mastic, Myrrh, Peru Balsam, Sandarac, Storax, Tolu balsam, Tar, Coal tar
(vi) Fixed oils and fats	Arachis, Castor, Chaulmoogra, Coconut, Cottonseed, Linseed, Olive, Sesame, Almond, Theobroma, Lard, Cod liver, Halibut liver, Kokum butter
(vii) Waxes	Beeswax, Spermaceti, Carnauba wax
(viii) Volatile oil	Turpentine, Anise. Coriander. Peppermint, Rosemary, Sandalwood, Cinnamon, Lemon, Caraway, Dill, Clove, Eucalyptus, Nutmeg, Camphor

(continued)

Table 5.2 (continued)

Classification of drugs	Drug examples
(ix) Animal products	Beeswax, Cantharides, Cod-liver oil, Gelatin, Halibut-liver oil, Honey, Shark-liver oil, Shellac, Spermaceti wax, Wool Fat, Musk, Mylabris, Lactose
(x) Fossil organisms and minerals	Bentonite, Kaolin, Kiesselguhr, Talc

Table 5.3 Drugs are classified into phyla, orders, families, genera, species, sub-species

Phylum	Order	Family	Genus	Species
Gymnosperms	Gnetales	Ephedraceae	*Ephedra*	*E. sinica*
Angiosperm: Dicotyledons	Rhoedales Rhanales	Papaveraceae Rhamnaceae	*Papaver* *Zizyphus*	*P. somniferum* *Z. mauritiana*
Angiosperm: Monocotyledons	Glumiflorae Liliflore	Poaceae Liliaceae	*Cynodon* *Allium*	*C. dactylon* *A. sativum*

main characters of various taxa that contribute crude drugs, while Table 5.5 gives the taxonomical classification of some drugs.

Merits

Taxonomical classification allows for precise and ordered arrangement of drugs and accommodates any drug without ambiguity, and it is helpful for studying evolutionary development.

Demerits

This system does not correlate in between the chemical constituents and biological activity of the drugs. This system of classification is criticized for its failure to recognize the organized and unorganized nature of crude drugs and chemical nature of active constituents and therapeutic significance of crude drugs.

5.1.4 Pharmacological Classification

This pharmacological or therapeutic classification involves the grouping of drugs according to their pharmacological action of active constituents or their therapeutic uses, regardless of their morphology, taxonomical status, or chemical relationships. The drugs differing in mechanism of action but having same pharmacological effects are also grouped together, e.g., bulk purgatives, irritant purgatives, emollient purgatives. This classification is more relevant and is mostly followed method. Thus, drugs like digitalis, squill, and strophanthus having cardiotonic action are grouped together irrespective of their parts used, phylogenetic relationship, and the

Table 5.4 Main characters of various taxons that contribute crude drugs

Plant kingdom or *Plantae*	Characteristics
Non-vascular plants	
Thallophyta	(i) Algae and fungi are consider together (ii) They differ in mode of nutrition (iii) Algae exhibit autotrophic and fungi exhibit heterotrophic nutrition. Example: agar of Rhodophyta; sclerotium of *Claviceps purpurea* (Ascomycota)
Bryophyta	(i) Bryophytes are non-vascular embryophytes (land plants) (ii) Plants do not contain vascular tissues; some have specialized tissues for the transport of water (hydroids) (iii) Life cycles are dominated by the gametophyte stage (iv) Includes Hepaticea (Liverworts—Riccia, Marchantia), Anthocerotae (Anthoceros), and Musci (Mosses); example: *Sphagnum, Polytrichum*
Vascular plants	
Pteridophyta	(i) This group of plant derives its name from the fern, *Pteris,* which also represents salient features of the group (Pterido-*pteris*, Phyton-plant) (ii) They occur is humid and tropical climates and usually ground on soil, rocks, in ponds, etc. (iii) These plants are also raised in pots as ornamentals Example: Male fern
Gymnosperm	(i) The gymnosperm (gymnos-naked and sperma-seed, i.e., plant with a naked seeds) is comparatively more ancient than the angiosperm in evolutionary terms (ii) The living gymnosperms are widely distributed in the cold climates (iii) The plant body is sporophyte and differentiated into roots, stem, and leaves Example: Ephedra, Colophony
Angiosperm	(i) The term angiosperm means enclosed seed because the ovules or potential seed is enclosed within a hallow ovary (ii) The angiosperms constitute the most dominant and ubiquitous vascular plants of present-day flora (iii) Dicots and monocots are its subdivisions
Angiosperm	**Monocotyledons**—They have one cotyledon in the seed. Example: Vanilla, Colchicum
	Dicotyledons—They have two cotyledons in the seed. Example: Coriander, Capsicum

Angiosperms Phylum	Order	Family	Drugs
Monocotyledons	Liliflorae	Liliaceae Dioscoreaceae	Scilla Colchicum Asparagus Dioscorea

(continued)

Table 5.4 (continued)

Angiosperms Phylum	Order	Family	Drugs
Dicotyledons	Microspermae Papaverales Rosales Rutales Rhamnales Malvaies Umbelliflorae Gentianales Tubiflorae	Orchidaceae Papaveraceae Rosaceae Leguminosae Rutaceae Rhamnaceae Malvaceae Apiaceae Loganiaceae Gentianaceae Apocyanaceae Convolvulaceae Lamiaceae	Vanilla Opium Almond Quillaia Rose oil Balsam of Tolu Glycyrrhiza Senna Bael, Lemon Orange peel Cascara Bark Sida
	Plantaginales Dipsacates Campanulales	Solanaceae Scrophulariaceae Plantaginaceae Valerinanceae Lobeliaceae Asteraceae	Coriander Caraway Dill, Fennel Nux-vomica Chirata Rauwolfia Strophanthus Shankhpushpi (Convolvulus pluricaulis) Mentha Ocinuim Belladonna Solanaceae Capsicum Datura Hyoscyamus Figworts, mulleins Digitalis Plantago Valerian Lobelia Artemisia Costus or Kuth
Gymnosperms	Genetales Coniferae	Ephedraceae Finacea	Ephedra Colophony
Bryophyta and Pteridophyta (Liverworts, Mosses and Ferns)	Marchantiales Polytrichales Filicales	Marchantiaceae Polytrichaceae Polypodiaceae	*Marchantia* *Polytrichum* Male fern
Thallophyta (Bacteria, Fungi, Lichens) Rhodophyta	Gelidiales	Gelidiaceae	Agar

Table 5.5 Taxonomical classification of some crude drugs

Phyllum	Order	Family	Drugs
Thallophyta (Algae, Fungi, Lichens)	Gelidiales Hypocreales Lecanorales	Gelidiaceae Clavicipitaceae Parmeliaceae	Agar ergot *Usnea* spp.
Bryo- and Pteridophyta (Liverhorts, Mosses and Ferns)	Marchantiales Sphagnales Dryopteridales	Marchantiaceae Sphagnaceae Dryopteridaceae	Marchantia Sphagnum Dryopteris/male fern
Gymnosperms	Genetales Coniferae	Ephedraceae Pinaceae	Ephedra Colophony
Angiosperms (Monocotyledons)	Liliflorae Microspermae	Liliaceae Dioscoreaceae Orchidaceae	Colchicum Dioscorea Vanilla
Angiosperms (Dicotyledons)	Rosales	Fabaceae	*Glycyrrhiza glabra*, *Astragalus gummifer*, Myroxylon balsamum
	Tubiflorae	Solanaceae	Atropabelladonna, Hyoscyamusniger, Daturastramonium

nature of phytoconstituents they contain. Table 5.6 gives an outline of pharmacological classification of drugs.

Merits

This system of classification can be used for suggesting substitutes of drugs if they are not available at a particular place or time.

Demerits

Drugs having different action on the body get classified separately in more than one group that causes ambiguity and confusion. Cinchona is an antimalarial drug because of the presence of quinine, but can be put under the group of drug affecting heart because of antiarrhythmic action of quinidine.

But purely pharmacological classification for herbal materials is difficult because of the numerous conditions for which any one traditional method may be employed. Based on the pharmacological response, the herbal medicines can be grouped under the following categories. Some of the major pharmacological groupings include herbal medicines which act on the nervous systems, the heart and blood vessel, the lungs, the gastrointestinal tract, the kidneys, the skin, and mucus membranes. Other categories include hormones (steroids), vitamins, and chemotherapeutic medicines used for the treatments of infections and malignant diseases. All these may also be classified as (a) systemic (function through the organized systems) and (b) non-systemic (localized action) medicines.

Table 5.6 Classification of drugs based on pharmacological action

Pharmacological or therapeutic classes	Name of drugs
Malignant growth inhibitors	
1. Anticancer (suppresses malignant growth)	1. Vinca, Podophyllum, Taxus, Camptotheca
2. Antiinflammatory (suppresses inflammation)	2. Colchicum corm and seed, turmeric
Drugs acting on gastrointestinal tract	
3. Bitter principles	3. Gentian, Quassia, Cinchona, Nux-vomica, Gentian, Picrorhiza, Chirata, Kalmegh
4. Carminatives (relieves flatulence or excess gas in the stomach or bowels)	4. Dill, Mentha, Gentian, Cinnamonbark, Cardamom seed
5. Emetics (a drug that causes vomiting)	5. Ipecacuanha
6. Antiamoebic (suppresses amoebic infection)	6. Ipecac root, Kurchi bark
7. Bulk laxatives (looses bowels and relieves constipation)	7. Agar, Ispaghula, Banana
8. Purgatives (evacuates bowels)	8. Senna, Castor oil, Cascara bark, Rhubarb, Aloe, Plantago seed husk
9. Peptic ulcer	9. Derivatives of Glycyrrhetinic acid (Liquorice and Raw banana)
10. Antiasthmatic (corrects bronchial disorder)	10. Ephedra, Lobelia, Vasaka, Tylophora
11. Anthelminthic (kills intestinal parasitic worms)	11. Male fern, Quassia wood, Artemisia, Vidang, Chenopodium oil
Antispasmodic (*cures convulsion or tonus of pain muscle*)	
12. Smooth Muscle Relaxants	12. Datura, Hyoscyamus, Belladonna; Opium, Datura, Hyoscyamus
13. Skeletal Muscle Relaxants	13. Curare
14. Astringent (styptic, stop bleeding)	14. Catechu, Tannic acid, Myrrh, Myrobalan, Ashoka bark
15. Analgesic (relieves pain, reduces temperature)	15. Opium, poppy, Cannabis
16. Flavors	16. Nutmeg fruit, Clove, Umbelliferous fruits, Peppermint, Saffron, Asafoetida, Oleo-gum resin. Mint, Tulsi, Ginger, Vanilla
Drugs acting on respiratory system	
17. Expectorant (relieves cough from the lung)	17. Senna, Rhubarb, Benzoin, Balsam of Tolu, Glycyrrhiza, Vasaka, Tulsi
18. Antiexpectorant	18. Stramonium leaves (Atropine)
19. Antitussives (prevents or relieves cough)	19. Opium (Codeine, Noscapine)
20. Brochodilator (dilates bronchi and bronchioles)	20. Ephedra, Tea (Theophylline)

(continued)

Table 5.6 (continued)

Pharmacological or therapeutic classes	Name of drugs
Drugs acting on cardiovascular systems	
21. Cardiotonic	21. Digitalis, Squill, Strophanthus
22. Cardiac depressants	22. Cinchona (quinidine), Veratrum
23. Vaso-constrictors (causes constriction of blood vessels)	23. Ergot (ergotamine), Ephedra
24. Tranquilizers (reduce anxiety), Antihypertensives (reduce blood pressure)	24. Rauwolfia Roots, Cocaine, Cannabis
Drugs acting on autonomic nervous systems	
25. Adrenergics	25. Ephedra
26. Cholinergics (related to choline and liver function)	26. Physostigma, Pilocarpus
27. Anticholinergics	27. Belladonna, Datura
Drugs acting on CNS	
28. CNS stimulants	28. Coffee (caffeine)
29. Analeptics	29. Nux-vomica, Lobelia, Camphor
30. CNS depressants	30. Hyoscyamus, Belladonna, opium
31. Hallucinogenics (cause error in perception)	31. Cannabis, Poppy latex
32. Antirheumatics (relieve the pain of rheumatism)	32. Aconite, Colchicum, Guggul

(a) **Systemic**

(i) Medicines act on the automatic nervous system;
(ii) Medicines act on the central nervous system;
(iii) Medicines act on the heart muscle;
(iv) Medicines act on the blood vessels;
(v) Promotion of diuresis (in case renal flow);
(vi) Action on the respiratory system;
(vii) Action on the gastrointestinal tract;
(viii) Action on the liver; and
(ix) Action on the uterus.

(b) **Non-systemic**

(i) Action on the skin and mucous membranes;
(ii) Action on sugar metabolism;
(iii) Steroids and antiinflammatory drugs;
(iv) Treatment of malignant diseases;
(v) Treatment of infections;
(vi) Treatment of allergies; and
(vii) Vitamins.

Drugs are either (i) pure chemicals, such as sodium bicarbonate or potassium iodide; (ii) mixed mineral products, such as petroleum oil, vaseline, or ichthyol; or (iii) certain animal or plant parts or products. Of animal nature or origin are musk, cantharides, adrenaline, lard, honey; of plant nature or origin are herbs, barks, roots, leaves, fruits, seeds, resins, alkaloids, etc.

5.1.5 Chemical Classification

The biological activity of a drug is due to the presence of certain chemical constituents in it. Plants and animals synthesize chemical compounds such as fats, carbohydrates, proteins, volatile oils, alkaloids, and resins, and some of these are pharmacologically active constituents. A single active constituent may be isolated from the crude drug and used as a medicinal agent. More than 75 pure compounds derived from higher plants find their place in modern medicine. For example, the important traditional active drug principles are codeine, atropine, ephedrine, hyoscyamine, digoxin, hyoscine, digitoxin, pilocarpine, theobromine, theophylline, quinidine, quinine, emetine, caffeine, papaverine, and colchicine. These active constituents are differentiated from the inert compounds like starch, cellulose, lignin, and cutin.

According to this system, the crude drugs are divided into different groups on the basis of the chemical nature of important constituent. Since the pharmacological activity and therapeutic significance of crude drugs are based on the nature of their chemical constituents, the chemical classification of drugs is dependent upon the grouping of drugs with identical constituents. An out of this classification is as follows (Table 5.7):

Merits
It is a popular approach for phytochemical studies. The chemical classification of crude drugs seems to be the preferred method of study, since biological activities of crude drugs (therapeutic and pharmacological activities) are based on the chemical constituents of crude drugs.

Demerits
Ambiguities arise when particular drugs possess a number of compounds belonging to different groups of compounds, i.e., drugs which contain two or more types of chemical constituents cannot get appropriate placement by this system.

Table 5.7 Classification of drugs on the basis of chemical nature

	Chemical constituents	Drugs
1.	**Carbohydrates** Carbohydrates are polyhydroxy aldehydes or ketones containing an unbroken chain of carbon atoms (i) Gum (ii) Mucilages (iii) Others	(i) Acacia, Tragacanth, Guargum, Sterculia (ii) Plantago seed (iii) Starch. Honey, Agar, Pectin; Pectin. Bael, Cotton
2.	**Glycosides** Glycosides are compounds which upon hydrolysis give rise to one or more sugars (glycone) and non-sugar (aglycone) (i) Anthraquinoneglycosides (ii) Saponins glycosides (iii) Cyanophore glycosides (iv) Isothiocyanate glycosides (v) Cardiac glycosides (Steroidal) (vi) Bitter glycosides	(i) Aloe, Cascara, Rhubarb, Senna (ii) Quillaia, Arjuna, Glycyrrhiza, Dioscorea (iii) Wild Cherry bark (iv) Mustard (v) Digitalis. Strophanthus, Squill, Scilia (vi) Gentian. Calumba. Quassia Chirata, Picrorhiza, Kalmegh
3.	**Tannins** Tannins are complex organic, non-nitrogenous derivatives of polyhydroxy benzoic acids	Pale Catechu, Black Catechu, Ashoka bark, Galls, Myrobalan, Behera, Amla
4.	**Volatile oils** Monoterpenes and sesquiterpenes obtained from plants	Cinnamon, Nutmeg, Fennel, Dill, Caraway, Coriander, Cardamom, Orange peel, Mint, Clove, Ginger, Valerian, Saffron, Banafsha, Tulsi, Anise, Lemongrass, Jatamansi
5.	**Lipids** (i) Fixed oils (ii) Fats (iii) Waxes	(i) Castor, Olive, Peanut, Almond, Shark liver oil (ii) Cottonseed, Theobroma (iii) Lanolin, Theobroma, Lanolin, Beeswax, Spermaceti
6.	**Resins and Resin combinations** Complex mixture of compounds like resinols, resin acids, resinotannols, resenes (i) Resins (ii) Glycosidal resins (iii) Oleo resins (iv) Oleo gum resin (v) Balsam	(i) Colophony (ii) Podophyllum, Jalap, Kaladana (iii) Capsicum, Ginger (iv) Asafbetida, Guggul (v) Storax, Tolu balsam, Peru balsam, Benzoin
7.	**Alkaloids** Nitrogenous heterocyclic compounds of plant origin (i) Pyridine and Piperidine (ii) Tropane (iii) Quinoline (iv) Isoquinoline	(i) Lobelia,Nicotiana, Areca nut, Anabasis,Sedum (ii) Coca, Belladonna, Datura, Hyoscyamus, Stramonium, Henbane (iii) Cinchona, Dictamnus (iv) Opium, Ipecacuhuna, Amaryllis, Lycoris

(continued)

Table 5.7 (continued)

	Chemical constituents	Drugs
	(v) Indole (vi) Amines (e.g. vincamine-monoterpenoid indole alkaloid) (vii) Purine (viii) Steroidal (ix) Diterpene (x) Phenanthrene	(v) Ergot, Nux vomica, Rauwolfla (vi) Catharanthus, Physostigma, Ephedra (vii) Tea, Coffee (viii) Holarrhena, Solanum, Veratrums (ix) Aconitum (x) Opium
8.	**Proteins and enzymes**	Gelatin, Yeast, Ficin, Papain, Casein, Trypsin
9.	**Vitamins**	Yeast, Shark liver oil, Shark liver oil, Amla, Oxytocin
10.	**Triterpenes**	Rasna, Colocynth
11	**Hormones**	Insulin

5.1.6 Chemotaxonomic Classification

The character most often studied in chemotaxonomy is secondary metabolites of pharmaceutical significance such as alkaloids, glycosides, and flavonoids. DNA hybridization, amino acid sequencing in proteins, and serotaxonomy are also gaining significance in this method of classification. This system of classification relies on the chemical similarity of a taxon, i.e., it is based on the existence of relationship between constituents in various plants. There are certain types of chemical constituents that characterize certain classes of plants (Solanaceae family contains tropane alkaloids, Apiaceae family contains volatile oil, Pinaceae family contains oleoresin, etc.). This gives birth to the entirely new concept of chemotaxonomy that utilizes chemical facts or characters for understanding the taxonomical status, relationships, and the evolution of the plants. For example, tropane alkaloids, volatile oils, and oleoresin generally occur among the members of Solanaceae, Apiaceae, Pinaceae families, respectively, and thereby serve as a chemotaxonomic marker of respective family. The berberine alkaloid in Berberis and Argemone; rutin in Rutaceae members, ranunculaceous alkaloids among Ranunculaceae members, etc., are other examples. Thus, the chemical examinations of different plants have established that there is close link between their chemical constituents and taxonomical status. Chemotaxonomic classification is the latest system of classification and it gives more scope for understanding the relationship between chemical constituents, their biosynthesis, and their possible action.

Chemical characters show chemical relationship, in the same way as morphological characters show morphological relationships. The chemical characters have taxonomic value as they are stable, unambiguous, and not easily changeable. Phytochemical data are more basic and more privileged and are more indicative of

relationship than morphological characters. But it is laborious and needs extensive analytical work.

Information from different sources should be taken into consideration to get a satisfactory classification of crude drugs, and there is no obvious advantage in attaining overriding importance to any one type.

5.2 Classification of Modern or Allopathic Drugs

The term 'allopathy' refers to the principle of curing a disease by administering substances that produce the opposite effect of the disease when given to a healthy human. The classification of allopathic drugs used in the Western world based on the clinical usage is considered to be straight forward. Allopathic drugs may be grouped in the following way:

(a) Non-prescription drugs—Non-prescription drugs are the drugs, which can be purchased from a pharmacy without the prescription of a doctor. These drugs are also called as over-the-counter drugs.
(b) Prescription drugs—Prescription drugs require a prescription from a registered physician before they can be purchased at the pharmacy. These drugs are not sold over the counter. This distinction clearly indicates the importance of medical advice for drug use and is governed by legislation. Over-the-counter drugs are safe to use in most cases excepting deliberate misuse or abuse.

The anatomical therapeutic chemical (ATC) classification system, recommended by the World Health Organization (WHO 2005), categorizes drugs into 14 main classes according to the organ or biological system they act on as well as their therapeutic, pharmacological, and chemical properties. For example, (i) alimentary tract and metabolism, (ii) blood and blood forming organs, (iii) cardiovascular system, (iv) dermatologicals, (v) genitourinary system and sex hormones, (vi) systemic hormonal preparations, excluding sex hormones and insulins, (vii) antiinfectives for systemic use, (viii) antineoplastic and immunomodulating agents, (ix) musculoskeletal system, (x) nervous system, (xi) antiparasitic products, insecticides and repellents, (xii) respiratory system, (xiii) sensory organs, and (ivx) various.

Different Groups of Allopathic Medicines

Based on the properties and uses, the allopathic drugs are also classified as antibiotics, antacids, antigas medicines, wormicides, steroid medicines, medicines for the external uses, antiallergens and antihistamines, antihypertensive, antidiabetic, antidiarrheal medicines, laxatives, medicines for anti cold and cough, antiepileptic, antispasmodic, antipyretics, analgesics, antivomiting, antiulcer, hematinic, tranquillizers, medicines for guddiness, enzymes, vitamins, mineral compounds, amino acids, etc.

Some of the examples of non-prescription and prescription drugs are listed below:

(i) **Antihemorrhoid drugs**: Antihemorrhoid drugs are medicines that reduce the swelling and relieve the discomfort of hemorrhoids. Antihemorrhoid drugs are available as creams, ointments, and suppositories. Most can be bought without a physician's prescription.

(ii) **Topical antibiotics**: Allopathic medicines like topical antibiotics are getting unique importance in healing wounds and inflammation. Topical antibiotics are medicines applied to the skin to kill bacteria. Topical antibiotics help in preventing infections caused by bacteria that get into minor cuts, scrapes, and burns. For example, neomycin, silver sulfadiazine with chlorhexidine gluconate, and povidone-iodine are powerful ointments for healing wounds. Treating minor wounds with antibiotics allows quicker healing. If the wounds are left untreated, the bacteria will multiply, causing pain, redness, swelling, itching, and oozing. Most can be bought without a physician's prescription.

Other allopathic drugs for topical application include betamethasone combined with neomycin, gentamycin, miconazole, and beclomethasone dipropionate combined with gentamycin sulfate which are some steroid creams to overcome skin inflammations and diseases. Skin irritations and inflammations throughout the body can be controlled by the application of lindane lotion. Calamine and diphenhydramine lotion is useful to overcome the skin irritations due to sunburns, prickly heat, and insect bites. Diclofenac diethylamine and diclofenac sodium are effective in body and joint pain relief. Methyl salicylate is also combined with above said two compounds to have effective treatment. Ichthammol glycerine is also applied to get relief from pain at a particular point of our body. Clotrimazole, beclomethasone dipropionate, gentamycin sulfate, iodochlorhydroxyquinoline, chlorocresol, benzyl alcohol, methylparaben, and propylparaben are some of the medicines used in the manufacturing of skin creams to get rid of skin infections. The mixture of clindamycin phosphate USP, sodium methylparaben I.P, and sodium propylparaben I.P (erytop) is effective in controlling pimples and acne. Face wash before the application of above said face cream will be useful to have a good result.

(iii) **Antibiotics**: Antibiotics are medicines which arrest the growth of bacteria or fungi in the human body. Usually, they are available in various forms such as dispersible tablets, capsules, syrups, drops, injections, and dry syrups. Penicillin (*Penicillium*) and streptomycin (*Streptomyces*) are two known antibiotics of fungal origin. A large varieties of antibiotics widely used as allopathic drugs are known including amoxycillin, ampicillin, cefadroxil, cephalexin, cloxacillin, tetracycline, gentamycin, erythromycin stearate, sulfamethoxazole, trimethoprim, norfloxacin,

ofloxacin, cefixime, cefpodoxime proxetil, gatifloxacin, rifampicin, isoniazid, metronidazole, etc.

Most of the antibiotics are combined with antiallergic medicines like cetirizine hydrochloride and chlorpheniramine maleate to get good result and to ensure our safety. Ampicillin and amoxycillin are combined with cloxacillin to get more effect when they are taken for curing bacterial infections. Sulfamethoxazole, trimethoprim, and norfloxacin are effective in controlling the urinary tract infections (many people will get allergic problem with sulfa drugs). Rifampicin and isoniazid are effective in controlling tuberculosis caused by mycobacteria. Amoxycillin and ampicillin are commonly available in the strength of 250 and 500 mg. It is advisable to take lower strength of antibiotics to ensure our basic immunity power.

(iv) **Cough suppressants**: Cough suppressants are medicines that prevent or stop coughing. Cough suppressants act on the center of the brain that controls the cough reflex. They are meant to be used only to relieve dry, hacking coughs associated with colds and flu. They should not be used to treat coughs that bring up mucus or the chronic coughs associated with smoking, asthma, emphysema, or other lung problems. Chlorpheniramine maleate, ammonium chloride, and sodium citrate are the effective formula to control cough. Sometimes, chlorpheniramine maleate is replaced by diphenhydramine hydrochloride to get another formula. Dextromethorphan hydrochloride, phenylpropanolamine hydrochloride, and triprolidine hydrochloride are other mostly used things for cough formula. To overcome dry irritating cough, guaifenesin is combined with salbutamol sulfate. The combination of codeine phosphate 10 mg I.P and chlorpheniramine maleate 4 mg I.P in syrup form is finding nice result in controlling dry cough. Terbutaline sulfate and bromhexine hydrochloride are also used to control cough problem in the allopathic medication. Most can be bought with a physician's prescription.

(v) **Antiacne drugs**: Antiacne drugs are medicines that help clear up pimples, black heads, white heads, and more severe forms of acne. Different types of antiacne drugs are used for different purposes. For example, lotions, soaps, gels, and creams containing benzoyl peroxide or tretinoin may be used to clear up mild to moderately severe acne. Isotretinoin is prescribed only for very severe, disfiguring acne.

(vi) **Non-steroidal and steroidal antiinflammatory drugs**: Non-steroidal antiinflammatory drugs are medicines that relieve pain, swelling, stiffness, and inflammation. Non-steroidal antiinflammatory drugs (NSAIDs) are prescribed for a variety of painful conditions, including arthritis, bursitis, tendinitis, gout, sprains, strains, and other injuries. Non-steroidal antiinflammatory drugs relieve pain, stiffness, swelling, and inflammation, but they do not cure the diseases or injuries

responsible for these problems. Physician's prescription is necessary for dispensing such drugs.

Salbutamol, betamethasone, theophylline, and dexamethasone are some of the steroid drugs with antiinflammatory effects. They can reduce inflammative conditions such as redness, swelling, and soreness. They are also helpful for many conditions such as asthma and arthritis. They come in pills, sprays, creams, and ointments. The creams and ointments of steroids are applied on skin to get rid of eczema and contact dermatitis. The side effects of steroid medicines are weakening bones, thinning of skin, and increasing blood sugar level. They also affect liver when excessively used. When salbutamol (asthalin inhaler) inhaled, it is very important to have self control in dosage, and beyond limit, it may affect heart.

(vii) **Antiseptics**: Antiseptics are medicines that slow or stop the growth of germs and help prevent infections in minor cuts, scrapes, and burns. Antiseptics are applied to the skin to keep bacteria from getting into wounds and causing infection. Although antiseptics do not usually kill bacteria, they do weaken them and slow their growth. Simply applying an antiseptic to a wound is not adequate treatment. The wound should be cleaned first, and in most cases, it should be covered with a bandage or other type of dressing to keep it clean and moist while it heals. However, some antiseptics, such as phenol, can damage the skin if the wound is covered after they are applied. Some of the drugs can be bought without a physician's prescription.

(viii) **Laxatives**: These are the drugs for the condition of constipation, mostly needed by the sick and old people. These should be used only in the unavoidable condition. One should not get addicted to these medicines. To correct motion in the natural way, we need only vitamins and amino acids. Bisacodyl 5 mg I.P in tablet form is useful for the treatment. Liquid paraffin and milk of magnesia are other liquid forms of laxatives.

(ix) **Antiepileptic medicines**: It is not a disease, but a sign of problem in the brain which is causing a disruption in the brain's normal electrical activity. It may occur in any age in either sex. The condition is called as 'fits.' Phenobarbitone (30 or 60 mg) I.P (gardinol), sodium valproate 200 mg I.P (valparin), carbamazepine 200 mg I.P, (tegretol), pentoxifylline B.P 400 (trental) mg, etc., are some of the antiepileptic medicines.

(x) **Analgesics**: Analgesics are medicines that relieve pain. Analgesics are prescribed to relieve pain of all sorts—headaches, backaches, joint pain, sore muscles, and pain that results from surgery, injury, or illness. Among the most common analgesics are aspirin, choline salicylate, magnesium salicylate, and sodium salicylate. Ibuprofen, naproxen sodium, and ketoprofen are non-steroidal antiinflammatory drugs (NSAIDs). NSAIDs relieve pain and also reduce inflammation. Another common analgesic, acetaminophen provides pain relief but does not reduce inflammation.

(xi) **Antispasmodic medicines**: Dicyclomine hydrochloride 100 mg I.P (cyclopam), hyoscine butylbromide 10 mg I.P (buscopan), and chlordiazepoxide 10 mg I.P (librax) are used for the stomach pain. Of which dicyclomine hydrochloride 100 mg I.P is combined with nimesulide 100 mg I.P and mild dose of B complex vitamin to control mensural pains for ladies.

(xii) **Decongestants**: Decongestants are medicines used to relieve nasal congestion (stuffy nose). A congested or stuffy nose is a common symptom of colds and allergies. This congestion results when membranes lining the nose become swollen. Decongestants relieve the swelling by narrowing the blood vessels that supply blood to the nose. This reduces the blood supply to the swollen membranes, causing the membranes to shrink.

(xiii) **Salicylates**: Salicylates are medicines that relieve pain and reduce fever. Aspirin belongs to this group of drugs. Other members of this group include sodium salicylate, choline salicylate, and magnesium salicylate. Aspirin is used to relieve many kinds of minor aches and pains—headaches, toothaches, muscle pain, menstrual cramps, the joint pain from arthritis, and aches associated with colds and flu. Aspirin is also known as acetylsalicylic acid.

(xiv) **Vasodilators**: Vasodilators are medicines that act directly on muscles in blood vessel walls to make blood vessels widen (dilate). Vasodilators are used to treat high blood pressure (hypertension). By widening the arteries, these drugs allow blood to flow through more easily, reducing blood pressure. Amlodipine, nifedipine, atenolol, and reserpine are some of the medicines used for hypertensive condition. These medicines block the transport of calcium into the smooth cells lining the coronary arteries and other arteries of the body. Since calcium is important in muscle contraction, blocking of calcium transport relaxes artery muscles. So these medicines are helpful to cure chest pain called as angina. Dizziness, muscle and stomach pain, and head ache are some of the side effects of these medicines.

(xv) **Antidiabetic drugs**: Diabetes is caused by the lack of secretion of insulin hormone from pancreas. The lack of insulin affects sugar metabolism and a considerable rise in blood sugar level. Some of the medicines taken for diabetes are as follows:
Sulfonylureas group of medicines (acetohexamide, chlorpropamide, glipizide, glyburide, etc.) help the body to make more or required insulin. Metformin helps control sugar by optimizing the body use of insulin and by reducing the amount of sugar that the body absorbs from food. Thiazolidinediones, pioglitazone, and rosiglitazone help the body use insulin better alike metformin and also helpful to produce less sugar when the food taken. Meglitinides help the body to make more insulin; nateglinide and repaglinide are usually taken with meals. Alpha-glucosidase inhibitors help the body absorb sugar more slowly

and keep the level of the sugar in normal. These are taken every time after the meals. Acarbose and miglitol are two kinds of medicines in this group. Glibenclamide is available in pills form in 5 mg strength, commonly prescribed for the initial stage of diabetes. Side effects are nausea and allergic reactions. This medicine should be avoided in case of severe dysfunction of liver and kidney, pregnancy, and breast feeding.

(xvi) **Antacids**: Antacids are medicines that neutralize excess acid in the stomach. Overeating and improper and missing diets are some reasons for the secretion of excess acid in the stomach. Antacids are used to relieve acid indigestion, sour stomach, gastric problems, peptic ulcers, and heartburn. Antacids contain ingredients such as aluminum hydroxide, calcium carbonate, magnesium hydroxide, and sodium bicarbonate, alone or in various combinations. Some antacid products also contain the ingredient simethicone to relieve gas. Antacids are taken by mouth and work by neutralizing excess stomach acid. They are available in both tablet and gel form.

(xvii) **Expectorants**: Expectorants are drugs that loosen and clear mucus and phlegm from the respiratory tract. Guaifenesin is an ingredient in many cough medicines, such as Anti-Tuss, Dristan Cold and Cough, Guaifed, Guai Cough, and some Robitussin products. Some products that contain guaifenesin are available only with a physician's prescription; others can be bought without a prescription. They come in several forms, including capsules, tablets, and liquids.

(xviii) **Antifungal drugs**: Fungi cause fungal infections. These fungi surround us and frequently land on our skin and are inhaled into our lungs. Many fungi are harmless, some cause minor and irritating infections, while a few can cause much more severe infections. People with compromised immune systems, such as AIDS and cancer patients, may be more susceptible to fungal infections than others. Antifungal drugs are used to treat fungal infections.

(xix) **Antiallergic and antihistamines**: Antiallergic drugs are used for relieving from allergic conditions. Allergy is a reaction of our immune system in response our body's contact with allergy making things called allergens. The allergens are not really harmful to all people. Naturally, our immune system, only in particular cases, wrongly decides that they are harmful. Antiallergic drugs include cetirizine hydrochloride, chlorpheniramine maleate, decongestant, antihistamines, antiinflammatory agents, and antileukotrienes. These antiallergy medicines can be consumed in the form of tablets, syrups, powder, and drops. When consumed, these antiallergic medicines support the immune system and improve its overall resistance against allergens. Antihistamines are drugs that block the action of histamine (a compound released in allergic inflammatory reactions) at the H1 receptor sites, responsible for immediate hypersensitivity reactions such as sneezing and itching. By inhibiting the activity of histamine, they can reduce capillary fragility,

which produces the erythema, or redness, associated with allergic reactions. They will also reduce histamine-induced secretions, including excessive tears and salivation. Antihistamines help stop allergy symptoms such as itchy eyes, sneezy, and runny nose. Sometimes, itchy rashes may also be helped by an antihistamine. Drowsiness, dry mouth, and blurry vision are some of the side effects of antihistamines. When taken, it is better to avoid driving, riding, and machinery operations.

(xx) **Antidiarrheal drugs**: Diarrhea is usually caused by the intake of contaminated food or drink with bacteria, virus, and parasites. Indigestion also will become the reason for the diarrhea. Loperamide 2 mg I.P is commonly used to overcome the condition. Quiniodochlor tablets (enteroquinol) are the other one to control diarrhea. Metronidazole 200 mg or in 400 mg is added with antidiarrheals to have quick arrest of diarrhea. To get relief from stomach pain, dicyclomine hydrochloride 100 mg I.P is added.

(xxi) **Antigas agents**: Antigas agents are medicines that relieve the uncomfortable symptoms of too much gas in the stomach and intestines. Phazyme and simethicone are some of the important medicines which are working against gas. They help relieve the symptoms by preventing the formation of gas pockets and breaking up gas that already is trapped in the stomach and intestines. Antigas agents are sold as capsules, liquids, and tablets (regular and chewable) and can be bought without a physician's prescription.

(xxii) **Smoking cessation drugs**: Smoking cessation drugs are medicines that help people stop smoking cigarettes or using other forms of tobacco. People who smoke cigarettes or use other forms of tobacco often have a difficult time when they try to stop. Most smoking cessation products contain nicotine, but the nicotine is delivered in small, steady doses spread out over many hours. Smoking cessation drugs that contain nicotine are also called nicotine substitution products or nicotine replacement therapy. These come in four forms—chewing gum, skin patch, nasal spray, and inhaler. Another type of smoking cessation drug, bupropion (zyban), also reduces craving and withdrawal symptoms, but it contains no nicotine.

(xxiii) **Enzymes**: These are the protein molecules which are naturally secreted from the pancreas to digest food. Pepsin I.P (1:3000) and α-amylase I.P (1:2000) are some of the important digestive enzymes. These are available in both capsule and liquid form. Lack of appetite, gastric problems, and indigestion needs enzymes.

(xxiv) **Wormicides**: Mebendazole and albendazole are important wormicides used in the allopathic medication. Mebendazole is used to overcome amebiasis, and albendazole is effective in vanishing worms found in human bowl and stomach. Albendazole is available in both chewable and liquid form. The people who are interested in nonvegetarian food

items need to use it to avoid worm problems. Loss of weight, lack of appetite, and anal itching are some of the symptoms of worm infections.

(xxv) **Vitamins**: Vitamins are very important for the essential activities of the body. Vitamin A, B complex (B1, B2, B6, B12), C, D, E, and K are some of the important vitamins used in the allopathic medication. Generally, vitamins are available in the form of capsules, tablets, syrups, and injections. They are used either separately or in mixed form. Vitamin A, retinol, is a growth-promoting and antiinfectant vitamin. It is naturally available in carrot, cabbage, grapes, fishes, and cod-liver oil. It is available in tablet and liquid form. Vitamin A increases appetite and sexual desire. Sight problem, skin problem, body weakness, and nervous complaint can be prevented by the addition of vitamin A. Vitamin B complexes are neurotrophic vitamins. They increase appetite. Vitamin B1 (thiamine mononitrate) and vitamin B2 (riboflavine) are used in the treatment of mouth ulcers. Vitamin B6 (pyridoxine hydrochloride) is taken for general health and good natural sleep. Vitamin B12 (cyanocobalamine) is obtained from animal part and used for having good body health and widely used in injection form. Vitamin C (ascorbic acid) is naturally found in citrus fruits, vegetables, and spices like pepper. It is useful to get rid of scurvy disease. It increases appetite and being an antioxidant keeps the health of skin and provides the young looking. Vitamin D (secosteroids—ergocalciferol, cholecalciferol, etc.) may be produced in the skin, specifically cholecalciferol from cholesterol in the presence of evening sunshine (hence its nickname, the 'sunshine vitamin'), and it is helpful to the growth of bones. Vitamin E (tocopheryl acetate) is, important for sexual and skin health, naturally available in badam nuts. Vitamin K (K1-phylloquinone, K2-menaquinone) is needed for the blood clotting in case of severe wounds and thus helps to avoid the loss of blood.

(xxvi) **Mineral compounds**: A variety of mineral salts are used in the medicine world. Ferrous gluconate, calcium carbonate, magnesium oxide, manganese sulfate, copper sulfate, zinc sulfate, sodium borate, and sodium molybdate are some of them. Calcium carbonate is used for the growth of the bones. Ferrous gluconate is used to overcome anemic problem, and it is combined with other minerals and vitamins when in use. Zinc sulfate is also very important for the health, and it induces sexual desire and increases immunity power. Sodium chloride, potassium chloride, and sodium nitrate are used to prepare salt mixture to overcome tiredness and dehydration because of diarrhea. Excess loss of minerals can be adjusted by the addition of this salt mixture dissolving in the ratio of 4.2 gm/200 ml of water. Sodium chloride and dextrose are used to prepare saline water for injection through veins.

(xxvii) **Amino acids**: Amino acids are essential for our nervous system. They increase our memory power, general health, and appetite. Alanine, arginine, asparagine, aspartic acid, cysterine, glutamic acid, glutamine,

glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine are required amino acids in daily food. There are about 20 varieties of amino acids in the medical science. Unlike fat and starch, these acids cannot be stored by our body for longer use. It is necessary to take enough amino acids in on regular basis.

(xxviii) **Antipyretics**: These are body temperature reducing medicines in case of high fever. Paracetamol, mefenamic acid, and nimesulide are some of the common antipyretics used in the allopathic world. These things work well when taken along with warm water. The over dose of paracetamol and nimesulide is susceptible to make liver and kidney problems, respectively. However, the adequate water drinking will be helpful to avoid such risks.

(xxix) **Analgesic medicines**: These are all body pain killer medicines. Paracetamol, ibuprofen, nimesulide, mefenamic acid, diclofenac sodium, diclofenac potassium, serapeptidase, aceclofenac, and chlorzoxazone are some of the important pain killers. These medicines are usually combined with neurotrophic vitamins, B complex, to have better result. Paracetamol suits well for headaches and nimesulide for tooth ache and body pain. Diclofenac sodium and serapeptidase are used for total body pain. Diclofenac potassium and chlorzoxazone are given for arthritis.

(xxx) **Antivomiting medicines**: Some people may be suffering from vomiting during their travelling time. Promethazine theoclate 25 mg I.P (avomine) is used to overcome vomiting problem during the travel; vomiting accompanied with fever can be cured by the intake of metoclopramide 10 mg I.P, nimesulide 100 mg I.P and ibuprofen + paracetamol tablets. Domperidone 10 mg is also taken instead of metoclopramide to cure vomiting.

(xxxi) **Antiulcer medicines**: Excess acid secreted because of overeating and missing of diets in correct time are the main reasons for ulcer problems. Indigestion associated with gas and heart burns is called as gastric ulcer. This condition is managed with antacid gel and ranitidine 150 mg I.P tablet. When the damages are found in the linings of stomach and small intestines because of the acidity, the condition will be called as peptic ulcer. Omeprazole 20 mg I.P or rabeprazole 20 mg I.P or pantoprazole 40 mg I.P or lansoprazole 30 mg I.P are accompanied with antacid and ranitidine tablets to get relief from peptic ulcer.

(xxxii) **Medicines for giddiness**: Prochlorperazine maleate 5 mg I.P, betahistine dihydrochloride 8 mg I.P (Vertin), and cinnarizine 25 mg I.P (Vertigon) are used to over come guddiness problems.

(xxxiii) **Tranquillizers**: Tranquillizers are the medicines which induce or bring the sleeping condition of the body. Diazepam 5 or 10 mg I.P, nitrosum 5 or 10 mg I.P, and alprazolam 0.25 or 0.5 or 1 mg I.P are some of the tranquillizers used in the allopathic medication. These medicines should be never taken with liquors as the presence of liquors in our body will

send 10–15 times greater than the normal sleeping pulses sent to brain by these medicines.

(xxxiv) **Hematinic medicines**: These are helpful to increase hemoglobin level of blood in our body. 'Hem' refers iron and 'globin' refers protein part of the blood. These medicines are containing iron compounds such as ferrous gluconate, ferric ammonium citrate, and iron choline citrate with protein hydrolysate, vitamin C, and vitamin B complex. The hematinic medicines are available in the form of capsules, tablets, and syrups.

5.3 Nutraceuticals, Functional Food, and Cosmeceuticals

Nutraceuticals and Their Classification

The term 'nutraceutical' was coined from 'nutrition' and 'pharmaceutical' in 1989 by Stephen L. De Felice (Jack 1995; Mannion 1998) and was originally defined as 'a food (or part of the food) that provides medical or health benefits, including the prevention and/or treatment of a disease' (Brower 1998; Kalra 2003, Trottier 2010). A nutraceutical may be a naturally nutrient-rich food (e.g., spirulina, garlic, soy) or a specific component of a food (e.g., omega-3 fatty acids, lycopene, saponins). They are also known as medical foods, 'designer foods,' nutritional supplements, and dietary supplements and include a number of substances ranging from natural diets, herbal products, biofortified crops, and genetically modified and processed food products such as cereals, soups, and beverages. Nutraceuticals can deliver benefits beyond basic nutrition and provide health benefit, modulate immunity, and/or prevent and cure specific diseases. The ability of nutraceuticals to influence chronic diseases (e.g., diabetes, cancers) has been recognized, and they will play important role in future therapeutic development. In addition, it is also claimed that nutraceuticals delay the aging process, increase life expectancy, or support the structure or function of the body. Herbal nutraceutical is useful in maintaining health, and it works against nutritionally induced acute and chronic diseases and promotes optimal health, longevity, and quality of life (Chauhan et al. 2013).

Nutraceuticals have received considerable interest because of their presumed safety and potential nutritional and therapeutic effects (Rajasekaran et al. 2008). People can improve their health by supplementation and by consuming foods that have been formulated or fortified. Another reason for the growing trend of nutraceuticals is public education, renewable source, cultivation and processing, environmental friendliness, and local availability (Keservani et al. 2010). UK, Germany, and France were the first who considered that diet is more important factor than exercise or hereditary factors in achieving a good health. Canada defined them as 'a product produced from foods but sold in pills, powders, (potions) and other medicinal forms not generally associated with food.' In India, nutraceuticals are the food components made from herbal or botanical raw materials, which are used for preventing or treating different types of acute and chronic maladies (Thakur et al. 2010).

Commercial nutraceuticals have to pass through strict regulatory controls for quality and positive health impact.

Classification of Nutraceuticals

Nutraceuticals are classified as traditional or natural nutraceuticals (e.g., nutrients, herbals, phytochemicals, probiotic picroorganisms, nutraceutical enzymes) and non-traditional or artificial nutraceuticals (e.g., fortified and recombinant nutraceuticals).

1. **Traditional nutraceuticals**

Traditional nutraceuticals are simply natural with no changes to the food. Food contains several natural components that deliver benefits beyond basic nutrition, such as lycopene in tomatoes, omega-3 fatty acids in salmon, or saponins in soy. Traditional nutraceuticals are grouped on the basis of (a) chemical constituents: (i) nutrients, (ii) herbals, and (iii) phytochemicals; (b) probiotic microorganisms; and (c) nutraceutical enzymes.

(a) Chemical constituents

(i) Nutrients

Substances such as vitamins, minerals, amino acids, and fatty acids with established nutritional functions. Most vegetables, wholegrain cereals, dairy products, fruits, and animal products such as meat and poultry contain vitamins and are helpful in curing heart diseases, stroke, cataracts, osteoporosis, diabetes, and cancer. Minerals found in plant, animal, and dairy products are useful in osteoporosis and anemia; build strong bones, teeth, and muscles; improve nerve impulses and heart rhythm. Flax seed and salmon contain fatty acids omega-3 PUFAs and are potent controllers of the inflammatory processes, maintenance of brain function, and reduce cholesterol deposition.

(ii) Herbals

Nutraceuticals hold a great promise to improve health and prevent chronic diseases with the help of herbals. Some examples are willow bark (*Salix nigra*), having active component as salicin, which is antiinflammatory, analgesic, antipyretic, astringent, and antiarthritic (Ehrlich 2009). Parsley (*Petroselinum cripsum*) contains flavonoids (apiol, psoralen) and is diuretic, carminative, and antipyretic. Peppermint (*Mentha piperita*) contains menthol as an active component and cures cold and flu (Ehrlich 2009). Lavender (*Lavandula angustifolia*) contains tannin which is helpful in curing depression, hypertension, stress, cold, cough, and asthma. Cranberries (*Vaccinium erythrocarpum*) contain proanthocyanidin and are found to be useful in cancer, ulcers, and urinary tract infections.

(iii) Phytochemicals

Phytochemicals constitute a class of nutraceuticals. They are classified on the basis of chemical name given according to their phytochemical properties. For example,

carotenoids (isoprenoids) found in various fruits, vegetables, and egg yolk are anticarcinogenic; boost natural killer immune cells; and protect cornea against UV light. Legumes (chickpeas and soybeans), grains, and palm oil contain non-carotenoids, which remove cholesterol and are anticarcinogenic. Flavonoid polyphenolics are found in berries, fruits, vegetables, and legumes, which are potent antioxidants and phytoestrogens; prevent breast cancer and prostate cancer; and control diabetes. Non-flavonoid polyphenolics are present in dark grapes, raisins, berries, peanuts, and turmeric roots; are strong antiinflammatory, antioxidants, and effective anticlotting agents; and reduce cholesterol. Phenolic acids, found in blueberries, tomatoes, and bell peppers having antioxidant activity, reduce mutagenicity of polycyclic aromatic hydrocarbons. Seeds of *Barbarea verna*, broccoli contain isothiocyanates (glucosinolates) and have antitumorigenesis activity.

(b) Probiotic microorganisms

The scientific interest in probiotics boosted from the work of Metchnikoff to transform the toxic flora of the large intestine into a host-friendly colony of Bacillus bulgaricus was found by Hord (2008). 'Probiotics' mean 'for life' and are defined as live microorganisms, which when consumed in adequate amounts confer a health effect on the host (Michail 2006). They are friendly bacteria that promote healthy digestion and absorption of some nutrients. They act to crowd out pathogens, such as yeasts, other bacteria, and viruses that may otherwise cause disease and develop a mutually advantageous symbiosis with the human gastrointestinal tract (Holzapfel et al. 2001). They have an antimicrobial effect through modifying the microflora, preventing adhesion of pathogens to the intestinal epithelium, competing for nutrients necessary for pathogen survival, producing an antitoxin effect, and reversing some of the consequences of infection on the intestinal epithelium, such as secretory changes and neutrophil migration. Probiotics can cure lactose intolerance by the production of the specific enzyme (ß-galactosidase) that can hydrolyze the offending lactose into its component sugars (Pineiro and Stanton 2007). Some sources of probiotic microorganisms are mentioned in Table 5.8 (Holzapfel et al. 2001).

(c) Nutraceutical enzymes

Enzymes are an essential part of life, without which our bodies would cease to function. Those people who are suffering from medical conditions such as hypoglycemia, blood sugar disorders, digestive problems, and obesity eliminate the symptoms by enzyme supplements to their diet. These enzymes are derived from microbial, plant, and animal sources as given in Table 5.9:

2. **Non-traditional nutraceuticals**

Non-traditional nutraceuticals are artificial foods prepared with the help of biotechnology. Food samples contain bioactive components which are engineered

Table 5.8 Sources of probiotic microorganisms

Milk	Yoghurt	Fermented products	Human breast milk	GI tract	Vegetables/grains/fruits
Lactobacillus acidophilus, *L. lactis*	*L. delbrueckii subsp bulgaricus*	*L. casei*, *L. cellobiosus*, *L. curvatus*, *L. fermentum*, *L. helviticus*, *L. farciminis*	*L. reuteri*, *L. salivarius*	*L. gasseri*, *L. johnsonii*	*L. brevis*, *L. plantarum*
	Bifidobacterium adolescentis	*B. thermophilum*, *B. animalis*	*B. infantis*, *B. longum*, *B. breve*, *B. lactis*		
Propioni-bacterium freudenreichii	*Streptococcus thermophilus*	*Enterococcus faecium*, *Pediococcus acidilactici*		*Escherichia coli Nissle 1917*	*Leuconostoc mesenteroides*
					S. cerevisiae, *S. boulardii* Mushrooms

Table 5.9 List of nutraceutical enzymes from microbes, plants, and animals

Microbial enzymes/source	Plant enzymes/source	Animal enzymes/source
Hemicellulase (microorganisms and mushrooms)	Hemicellulase (plant walls)	Ox bile (ox)
Catalase	Pectinase (cell wall)	Pancrelipase (pancreatic juice)
Amyloglucosidase (ascomycetes)	α-Galactosidase (beans, cabbage, Brussels sprouts, broccoli, asparagus, other vegetables, and whole grains)	Trypsin (pancreatic juice)
Glucoamylase (*A. niger*, *Saccharomycopsis fibuligera*)	β-Amylase (higher plants)	Chymotrypsin (all classes of vertebrates)
Cellulase (all living cells)	Bromelain (pineapple)	Pepsin (animals tracheal secretions)
Invertase–Sucrase (yeast)	Biodiastase (soybean)	Lysozyme (saliva, tears, egg white, and many animal fluids)
Lactase–β-Galactosidase (bacteria)	Glucoamylase (callus and suspension cultures of sugar beets (*Beta vulgaris* L.) as well as in mature roots)	α–Amylase (saliva)

Source www.specialtyenzymes.com/

to produce products for human wellness. They are arranged into (i) Fortified nutraceuticals, (ii) Recombinant nutraceuticals, and (iii) Fortified nutraceuticals.

(i) Fortified nutraceuticals

It constitutes fortified food from agricultural breeding or added nutrients and/or ingredients, e.g., orange juice fortified with calcium, cereals with added vitamins or minerals, and flour with added folic acid. Some examples are milk fortified with cholecalciferol used in vitamin D deficiency (Casey et al. 2010). Prebiotic and probiotic fortified milk with *Bifidobacterium lactis* HN019 used in diarrhea, respiratory infections, and severe illnesses, in children (Sazawal et al. 2010). Banana fortified using soybean ferritin gene in iron deficiency was discovered by Kumar et al. (2011).

(ii) Recombinant nutraceuticals

Energy-providing foods such as bread, alcohol, fermented starch, yogurt, cheese, vinegar, and others are produced with the help of biotechnology. The production of probiotics and the extraction of bioactive components by enzyme/fermentation technologies as well as genetic engineering technology are achieved through biotechnology. Some of the products of recombinant organisms are shown in Table 5.10.

Table 5.10 Product produced by recombinant organisms (microorganisms, plants, and animals)

Product produced by recombinant microorganisms, plants, and animals			
A. Recombinant microorganisms			
Source	Enzyme	Products	References
Acetobacter xylinum	β-glucuronidase	Kombucha beverage	Malbasa et al. (2011)
Escherichia coli K-12	Chymosin	Milk-coagulated products	El-Sohaimy et al. (2010)
Fusarium venenatum	Xylanase	Increased bran solubilization	Sibbesen and Sorensen (2010)
Aspergillus oryzae	Esterase–lipase, aspartic proteinase, glucose oxidase, laccase, lipase, pectin esterase,	Alcoholic beverages (Sake, koji)	Ghorai et al. (2009)
Saccharomyces cerevisiae	Stilbene synthase and 4-coumaroyl-CoA	Resveratrol	White (2009)
Spirulina pacifica	Indoleamine 2,3-dioxygenase (IDO)	Increased hemoglobin	[www.nutraceuticalsworld.com/]

B. Recombinant plant			
Recombinant	Deficiency	Gene for recombination	References
Gold kiwifruit	Iron	High level of ascorbic acid, carotenoids lutein, and zeaxanthin	Beck et al. (2011)
Potatoes	Protein	Tuber-specific expression of a seed protein, *AmA1* (*Amaranth Albumin 1*)	Chakraborty et al. (2010)
Golden mustard	Vitamin A	Soybean *ferritin* gene	Chow et al. (2010)
Multivitamin corn	Multivitamin	Vitamins β-carotene corn (*Zea mays*) phytoene synthase (*psy1*) cDNA, ascorbate (rice dehydroascorbate reductase *(dhar*) cDNA, and folate *E. coli folE* gene encoding GTP cyclohydrolase (*GCH1*)	Naqvi et al. (2009)
Maize	Vitamin A (retinol)	Bacterial genes *crtB* and *crtI*	Aluru et al. (2008)
Tomato	Folate	Aminodeoxychorismate synthase (*AtADCS*)	de la Garza et al. (2007)
Golden rice	Vitamin A (retinol)	Two daffodil genes and one bacterial gene	Rockefeller Foundation www.rockfound.org
Iron rice	Iron deficiency	Soybean *ferritin* gene	[www.biotech.nature.com]

C. Recombinant animals			
Cattle	Human lysozyme	*rhLZ* expression vector *pBC2-HLY-NEOR*	Yang et al. (2011)
Yogurt	Probiotics microorganism	*Bifidobacterium lactis Bb-12* and *Lactobacillus acidophilus LA-5*	Allgeyer et al. (2010)
Cows	Lactoferrin deficiency	Recombinant human lactoferrin (rhLf)	Hyvonen et al. (2006)

Commercial Nutraceuticals

Many pharmaceutical companies are now trying to manufacture nutraceutical because there is undoubtedly a very huge and growing market. Nutraceuticals cover most of the therapeutic areas, such as antiarthritic, cold and cough, sleeping disorders, digestion and prevention of certain cancers, osteoporosis, blood pressure, cholesterol control, pain killers, depression, and diabetes. Recognition of health benefits from consumption of omega-3 rich seafoods is one of the most promising developments in human nutrition and disease prevention research in the past three decades (Pandey et al. 2010). Examples of some of the commercial nutraceutical manufacturers and their products name with expected claim are given below.

Bio Serae Laboratories of France manufactures 'Serenzo certified Organic' which constitutes citrus extract and acts as an antistress product; 'Resveravine' constitutes resveratrol and help in cardiovascular protection and antiaging properties [www.bioserae.com/]. Shotz Health of UK prepares 'Big Shotz' from ginseng, prebiotics rich in MEG-3 brand omega-3 EPA/DHA [http://www.nutraceuticalsworld.com/]. Guangzhou Lohas Biological Technology Co. Ltd. of China produces 'Ginseng KianpiPil' using reishi extract, ginseng extracts, and Rhodiola rosea extract as dietary supplement [www.company.indiatradepage.com/]. An Indian company, for example, La Casa Agrotech Private Ltd. manufactures 'Smrutihills' from Brahmi, Mandukaparni, as nervine tonic for mind and memory. SAB Herbals and Nutraceuticals assembles 'Methoxsalen Xanthotoxin Calcium Sennoside' from phytochemicals used in treating psoriasis, eczema, and vitiligo [www.hotfrog.in/Companies/].

Isha Agro Developers Pvt. Ltd. produces 'Imunohills' from amla, guduchi, and gokshura, which promotes cellular and humoral immunity. Bio Bodyfuelz Ltd. prepares 'PWR Sports' from *Sida cordifolia* extract which helps to boost endurance and refreshes muscles and 'Fat Burner' from cocoa beans extract (6% theobromine). Life Style Care produces 'Arctic Sea Super Omega' from olive oil and fish oil and is a rich source of omega-3 fatty acids and 'Forever Absorbent C' from bioflavonoids of oranges and papayas. Essential'z Energize Your Health manufactures 'Muscle Juice from protein blend' (whey protein isolate, whey protein concentrate, calcium caseinate, and egg white albumin) which feeds and nourishes the muscles. Amrutam Life Care Private Ltd. prepares 'Obexi' from *Boerhaavia diffusa* and is an antiobesity drug [www.trade.indiamart.com/].

Regulations

Food regulation is aimed at protecting the consumer's health, increasing economic viability, harmonizing well-being, and engendering fair trade on foods within and between nations. Commercial nutraceuticals have to pass through strict regulatory controls to provide a positive impact on an individual's health.

Functional Foods

There is no universally accepted definition of functional foods. Conventional foods generally satisfy nutritional function and hedonistic or sensory function of an individual, while functional foods fulfill specific physiological function beyond adequate nutritional effects in a way that is relevant to either an improved state of health and/or reduction in risk of disease. Functional foods can be considered to be those whole, fortified, enriched, or enhanced foods that provide health benefits beyond the provision of essential nutrients (Hasler 2002). Functional foods must remain foods and contain an ingredient (or fortified with an ingredient) like micronutrient or chemical with a beneficial effect on one or more target functions in the body beyond adequate nutritional effects (well-being or disease prevention); they must demonstrate their effects (or at least claim), and these effects can be expected to materialize when the food is consumed in normal amounts as part of the usual diet (but not be pills or capsules). A functional food can be a natural food, a fortified food, or a food from which a component has been removed by technological or biotechnological means, a food where the nature or bioavailability of one or more components has been modified, or any combination of these possibilities. A functional food might be functional for all members of a population or for particular groups of the population on the basis of age or genetic constitution.

There exists a direct relationship of diet to disease, and according to Willett (2002), over 60% of the risk of chronic diseases (e.g., heart disease, stroke, colon cancer, and type II diabetes) is potentially preventable by lifestyle modifications, including changes in diet. Based on the decades of scientific inquiry, the World Health Organization (WHO 2003) states that diet plays an important role in affecting the risk of a variety of chronic diseases and disorders (e.g., cancer, heart disease, type II diabetes, and obesity). There is continued interest in characterizing the contribution of diet to bone, joint, and eye health as well as to cognitive function. Increased consumption of fruits/vegetables is associated with a lowering of risk of a variety of cancers (Steinmetz and Potter 1996). For these and several other reasons (high healthcare costs, aging, health-conscious population, desire for healthy eating and lifestyle habits, changes in food regulations, numerous technological advances, growing marketplace for health-promoting products, etc.), interest in functional foods is growing worldwide. It is, however, not a new concept as the Ministry of Health, Labour and Welfare of Japan has been regulating Foods for Specified Health Uses (FOSHU) since 1080s with documented health benefits (Arai 1996; Nakajima 2004).

The foods might provide a therapeutic benefit is also not a new concept. The tenet, 'Let food be thy medicine and medicine be thy food,' was embraced ~2500 years ago by Hippocrates, the father of medicine. According to Roberfroid (2002), functional foods are generally part of a diet that provides health benefits beyond traditional nutritional effects. Functional foods have a potentially positive effect on health beyond basic nutrition. Functional foods promote optimal health and help reduce the risk of disease. For example, oatmeal is functional food because it contains soluble fiber that can help lower cholesterol levels and thereby reduce the risk of heart attack. Some foods are modified to have health benefits, e.g.,

orange juice that has been fortified with calcium for bone health. Health benefit is most likely due to the collective presence of many nutrient and non-nutrient plant components (a cocktail of phytochemicals). Glucosamine, calcium, and antiinflammatory and antioxidant nutrients, and phytochemicals are suggested for the improvement of joints, muscles, and bones. Role of xanthophylls (lutein) in eye health, conjugated linoleic acid (CLA) and tea phenolics in weight maintenance, and the balance between muscle mass and fatty tissue are suggested.

Consumption of refined and processed foods may trigger an immune response leading to inflammation which may contribute too many diseases and disorders from atherosclerosis to Alzheimer's disease. Some functional foods (e.g., fatty fish, whole grains, dark leaf greens, nuts, peppers, tomatoes, beets, ginger and turmeric, onions and garlic, and berries) with the help of their important minerals, fiber, vitamins, and other contents can reduce the risk of inflammation and many other diseases. Fatty or oily fish (e.g., salmon, tuna, sardines, and mackerel) is high in omega-3 fatty acids; whole grains (brown rice, steel cut oats, buckwheat and bulgur wheat) have more fiber than refined grains (white bread, white rice, and degermed cornmeal); dark leafy greens (e.g., broccoli, spinach, kale, collard greens, and rainbow chard) are a low-glycemic food, full of vitamin E, and have very high concentrations of minerals (Mg) and phytochemicals; almonds are full of fiber, vitamin E, calcium, omega-3s, and heart-healthy fat; bell peppers have capsaicin in them and are also full of important antioxidants; tomatoes are high in antioxidant and lycopene; beet root juice is high in antioxidants, fiber, vitamin C, and betalains; the antiinflammatory compound gingerol of ginger provides free radical protection, and curcumin of turmeric is a powerful antioxidant; berries (strawberries, blueberries, cranberries, etc.) are high in anthocyanins, the powerful antioxidants. They reduce the risk of inflammation, blood pressure, insulin spike, and many other diseases. Food products enriched for soy protein, plant sterols and stanols, omega-3 fatty acids, antioxidants, and fiber are being formulated and offered to the consumer (Meister 2002). The delivery of health benefits through functional food is a relatively new concept, and it is gaining in popularity in the society including producers (food industries) and consumers. However, the legal status with respect to food law is not yet well documented. Functional foods represent one of the most intensively investigated and widely promoted areas in the food and nutrition sciences today, but these are not magic bullets or panaceas for poor health habits (but diet), and linking the consumption of functional foods with health claims should be based on sound scientific evidence (Hasler 2002).

Scientists have identified the great majority of different physiologically active components in foods from plants (phytochemicals) and a few from animals (zoochemicals) or microbes that potentially could reduce the risk of a variety of chronic diseases. Characteristics of some functional foods available on the US market are shown in the following Table 5.11.

Like functional food, there are more terms for dietary products such as food supplements (or dietary supplements) and nutraceuticals (or nutriceuticals) that directly link nutrition with health.

Table 5.11 Strength of evidence for functional foods currently on the US market

Functional food	Bioactive component	Health benefit	Type of evidence	Strength of evidence	Recommended amount or frequency of intake	Regulatory status
1. Plant origin (phytochemicals)						
Fortified margarines	Plant sterol and stanol esters	Reduce total and LDL cholesterol	Clinical trials	Very strong	1.3 g/d for sterols 1.7 g/d for stanols	Health claim
Psyllium	Soluble fiber	Reduce total and LDL cholesterol	Clinical trials	Very strong	1 g/d	Health claim
Soy	Protein	Reduce total and LDL cholesterol	Clinical trials	Very strong	25 g/d	Health claim
Whole oat products	Glucan	Reduce total and LDL cholesterol	Clinical trials	Very strong	3 g/d	Health claim
Cranberry juice	Proanthocyanidins	Reduce urinary tract infections	Small number of clinical trials	Moderate	300 mL/d	Conventional food
Garlic	Organosulfur compounds	Reduce total and LDL cholesterol	Clinical trials	Moderate	600–900 mg/d	Conventional food or dietary supplement
Spinach, kale, collard greens	Lutein/zeaxanthin	Reduce risk of age-related macular degeneration	Epidemiological	Weak to moderate	6 mg/d	Conventional food or dietary supplement
Tomatoes and processed tomato products	Lycopene	Reduce risk prostate cancer	Epidemiological	Weak to moderate	Daily	Conventional food
Cruciferous, vegetables	Glucosinolates, indoles	Reduce risk of certain types of cancer	Epidemiological	Weak	3 or more servings/wk	Conventional food
Green tea	Catechins	Reduce risk of certain types of cancer	Epidemiological	Weak to moderate	Unknown	Conventional food

(continued)

Table 5.11 (continued)

Functional food	Bioactive component	Health benefit	Type of evidence	Strength of evidence	Recommended amount or frequency of intake	Regulatory status
2. Animal origin (zoochemicals)						
Fatty fish	(n-3) Fatty acids	Reduce TG, reduce heart disease cardiac deaths and fatal and non-fatal myocardial infarction	Clinical trials; epidemiological studies	Strong	2/wk	Qualified health claim for dietary supplements
Lamb, turkey, beef, dairy	CLA (conjugated linoleic acid)	Reduce breast cancer	In vivo and in vitro studies	Weak	Unknown	Conventional food
Fermented dairy products	Probiotics	Support GI (gastrointestinal) health, boost immunity	In vivo and in vitro studies, limited clinical data	Weak	Daily	Conventional food or dietary supplement

Source Hasler (2002)

Foods that have an FDA-approved health claim (sterol/stanol esters, oats, psyllium, soy) generally are supported by two dozen or more well-designed published clinical trials

Food supplements are concentrated sources of nutrients, dietary ingredients (including vitamins, minerals, amino acids, enzymes, glandulars, metabolites, organ, tissues, herbs, or other botanicals), or other substances with a nutritional or physiological effect whose purpose is to supplement the normal diet, available in the market in dose form (e.g., as pills, tablets, capsules, softgels, gelcaps, powders, extracts, or liquids in measured doses) taken by mouth and must not represent the product as a conventional food or a sole item of a meal or diet (EC 2007; FDA 2007).

Functional foods are similar in appearance to conventional foods and are consumed as part of a normal diet (Zeisel 1999), whereas the food supplements are not considered to be proper food. For nutraceuticals, the concept is less clear. A nutraceutical is a food or naturally occurring food supplement or part of a food that allegedly provides medicinal or health benefits, including the prevention and treatment of disease. A nutraceutical may be a naturally nutrient-rich or medicinally active food, such as garlic or soybeans, or it may be a specific component of a food, such as the omega-3 fish oil that can be derived from salmon and other cold-water fish.

A nutraceutical may be a product isolated or purified from foods, provides physiological benefit or protection against chronic disease, and is generally sold in medicinal forms not usually associated with foods (Canada 2007). Zeisel (1999) defines nutraceuticals as those diet supplements that deliver a concentrated form of a presumed bioactive agent from a food, presented in a nonfood matrix, and used to enhance health in dosages that exceed those that could be obtained from normal foods. The definition of nutraceuticals may be limited to natural, bioactive chemical compounds that have health-promoting, disease-preventing, or medicinal properties, or the concept may be extended by adding the category of medicinal foods (e.g., transgenic plants for oral vaccination against infectious diseases) to the other two nutraceutical categories of dietary supplements (e.g., vitamins, minerals, and plant extracts) and functional foods (e.g., omega-3 milk, cholesterol reducing oils and fats). According to these definitions, there is a clear distinction between functional food and food supplements, while nutraceuticals can cover functional food and food supplements, i.e., both functional food and food supplements could be considered nutraceuticals—as long as they can be derived from natural sources.

Classification of Functional Foods

Functional food may be classified into several groups on the basis of (i) food group it belongs to (e.g., dairy products, beverages, cereal products, confectionary, oils, and fats); (ii) the diseases it is expected to prevent or alleviate (e.g., diabetes, osteoporosis, colon cancer); (iii) its physiological effects (e.g., immunology, digestibility, antitumor activity); (iv) the category of its specific biologically active ingredients (e.g., minerals, antioxidants, lipids, probiotics); (v) its physicochemical and organoleptic properties (e.g., color, solubility, texture); or (vi) the processes that are used in its production (e.g., chromatography, encapsulation, freezing) (Juvan et al. 2005).

The Future of Functional Foods

According to the Department of Health and Human Services, diet plays a role in 5 of 10 of the leading causes of death, including coronary heart disease (CHD), certain types of cancer, stroke, diabetes (noninsulin dependent or type 2), and atherosclerosis. The dietary pattern characterized by high total and saturated fat, cholesterol, sodium, and refined sugars and low unsaturated fat, grains, legumes, fruits, and vegetables has been linked with these major causes of death in many developed countries including the USA. It has been suggested that consumption of certain foods or their associated physiologically active components may be linked to disease risk reduction (Hasler 1998).

Extensive research activities by academic, government, and private research institutes across the world are currently going on to understand and explore the mechanism of action of functional foods against chronic diseases of consumers. Nutrigenomics, following the results of human genome sequence, will have a profound effect on future functional foods research and development and also on future disease prevention efforts including the future of the functional foods industry (Fogg-Johnson and Meroli 2000; Anonymous 2001). Biotechnology will also influence the future of functional foods (Gura 1999). For example, development of genetically engineered iron-enriched rice and golden rice help prevent iron deficiency anemia and vitamin A deficiency-related blindness of millions of worldwide (Anonymous 2000). In the future, other foods enhanced with other nutritive or nonnutritive substances may even help to prevent chronic diseases such as heart disease, osteoporosis, or cancer (Falk et al. 2002; Pande et al. 2010).

Cosmeceuticals

The term 'Cosmeceutical' is a hybrid combination of cosmetics and pharmaceuticals. Cosmeceuticals have medicinal benefits (but not just used for beautification), which affect the biological functioning of the organ concerned depending upon the type of functional ingredients they contain. Cosmeceuticals are cosmetic products containing biologically active ingredients to add medical or drug-like benefits (e.g., cream, lotion, and ointment containing botanical, animal, and marine extracts like antioxidants, vitamins, peptides, essential oils, waxes, oils, natural color, natural fragrances, parts of plants like leaves). Cosmetics containing botanicals are herbal cosmetics, and for herbal cosmetics, permissible cosmetic ingredients are taken to form the base, and one or more herbal ingredients are added to it. Trees and herbs like *Azadirachta indica*, *Cocos nucifera*, *Aloevera* spp., *Camellia sinensis*, *Calendula* spp., *Carica papaya*, *Curcuma longa*, *Cymbopogon* spp., *Daucus carota*, *Emblica officinalis*, *Eucalyptus* spp., *Ginkgo biloba*, *Helianthus annuus*, *Lawsonia inermis*, *Rhodiola rosea*, *Rosea* spp., and similar many other herbs possess a vast and complex arsenal of bioactive phytochemicals (e.g., vitamins, antioxidants, oils and essential oils, hydrocolloids, proteins, terpenoids) that are able to calm or smooth, clean, restore, heal, and protect the skin and other parts of the body.

Examples of some of the zoochemicals used in cosmetics include the following: (i) hyaluronic acid, produced from rooster combs (fleshy growth or crest on the top of the head of gallinaceous birds), is used in antiaging skin care products as it is an antioxidant and a humectant and boosts collagen synthesis; (ii) carmine, a red dye made of red pigment from the crushed female cochineal insect, is often used in lipsticks, rouge, eye shadow, etc., and also used in food and drinks; (iii) most collagen in skin care creams comes from chicken feet and animal horns, and loss of collagen is one of the main signs of facial aging; (iv) glucosamine is derived from chicken bone marrow for the cosmetics industry; (v) ambergris from sperm whale is used in cosmetics as a fixative; (vi) fake vanilla fragrance comes from cow dung; (vii) placental protein comes from animal placenta; (viii) animal-derived stearic acid derived comes from waste animal tissue of cow, pig, and sheep; (ix) crystalline guanine, extracted from fish scales, is used to produce shiny effect in shampoo, eye shadow, and nail polish; panthenol, comes from meat or honey, is used in shampoos and conditioners to moisturize and lubricate hair; (x) keratin, hair care product, is extracted from horns, hooves, feathers, quills, and hair of various animals; and (xi) shellac, a resin secreted by the female lac insect, is used to create a shiny lacquer in products such as hairsprays, shampoos, mascara, and lipstick. Many of these chemicals are used as active ingredients of different cosmetic formulations for skin problems (like hyper pigmentation, skin wrinkling, skin aging, rough skin texture), hairspray, shampoo, etc.

Marine organisms including marine algae are rich sources of structurally diverse bioactive compounds like polyunsaturated fatty acids, pigments, and antioxidants for different biomedical products. A diverse group bioactive substances like terpenoids, carotenoids, tocopherol, phenolic compounds, polysaccharides (fucoidan, carrageenans, alginates, and agar), unsaturated fatty acids, mycosporine-like amino acids, and unsaturated fatty acids derived from marine algae are potential ingredients for cosmeceuticals (Agatonovic-Kustrin and Morton 2013). Many of these marine algae-derived compounds (vitamins, phytochemicals, enzymes, antioxidants, essential oils, etc.) are incorporated in skin care cosmeceuticals like creams, lotions, and ointments (Kim et al. 2008). These bioactive ingredients used in topical cosmeceuticals protect function like antioxidant, provide UV radiation protection, inhibit melanogenesis, immunomodulator, control of cutaneous bacterial flora, antiaging, antiwrinkle, antiviral, antiinflammatory, anticoagulant, antitumor, antihyperlipidemic agents, skin repair, skin hydration, gelling, and stabilizer. Functions of individual bioactive molecule or their group are given in Table 5.12:

Bioactive substances derived from marine resources have diverse functional roles as natural skin care agents, and these properties can be applied to the development of novel cosmetics as well as nutricosmetics from edible seaweeds and edible marine animals (Kim 2014).

The cosmeceuticals that are ingested orally are known as nutricosmetics. All these products are intended for the improvement of health and beauty of the skin and hair. They contain a wide spectrum of biologically active ingredients of natural origin including moisturizer, vitamin, sun protector, skin whitener, and free radical scavenger are nutritional supplements and support the function and the structure of

Table 5.12 Cosmeceutical application of compounds derived from marine algae

Bioactive component	Potential function as cosmeceutical	Other uses
1. Terpenoids	Photodamage, photoaging	
2. Carotenoids	UV filter, epidermal cells renewal, antioxidant, control of cutaneous bacterial flora	
3. Tocopherol	UV protection	
4. Phenolic compounds	UV protection	
5. Fucoidans	Antiaging, antiwrinkle	Antiviral, antiinflammatory, anticoagulant, antitumor
6. Carrageenans	Gelling and thickening	Antitumor, anticoagulant, immunomodulatory, antihyperlipidemic, induction of experimental inflammation and inflammatory pain, antiviral
7. Alginates	Face masks and body washes, skin repair, skin hydration, gelling, stabilizer	
8. Agars	Gelling, emulsifying	Bulking agent, laxative, anticoagulant, antioxidant
9. Unsaturated fatty acids	Antiaging, UV filters, antiwrinkle, regeneration, skin hydration	Antiinflammatory
10. Mycosporine-like amino acids	UV filters	

Source Agatonovic-Kustrin and Morton (2013)

the skin (e.g., vitamin C, omega-3 fatty acids, carotenes, flavonoids). Vitamin C functions as an antioxidant, reduces the impact of free radicals in the skin, and functions in the production of collagen in the dermis; omega-3 fatty acids and carotenes protect the skin from the damaging effects of ultraviolet light exposure, which may lead to accelerated skin aging and wrinkle formation (Katiyar 2002; Nichols and Katiyar 2010; Schagen 2012). Since 1990s, sales of nutricosmetics have increased dramatically to over 1 billion USD annually (Anonymous 2006). The various other terms by which cosmeceuticals can be substituted are active cosmetics, performance cosmetics, functional cosmetics, and dermaceuticals. Today's cosmeceuticals as well as nutricosmetics are serving as a bridge between personal care products and pharmaceuticals. The Cosmeceuticals are broad-spectrum topical agents that lie somewhere between pure cosmetics (lipstick and rouge) and pure drug (antibiotics and corticosteroids).

Classification of Cosmeceuticals

Cosmeceuticals are classified on the basis of their use into three categories as (a) skin cosmeceutical product (e.g., antiaging creams, moisturizers, facial products, and lotions); (b) hair cosmeceutical product (e.g., gel and creams, hair colorants and dyes, shampoos, growth stimulators, and conditioners); and (c) others (e.g., lipstick, nail polish, toothpaste, and powders). On the basis of the active ingredient content and function, cosmeceuticals are classified into eight categories as (a) retinoids (e.g., vitamin A, niacinamide, panthenol); (b) sunscreens (e.g., ferulic acid, enzophenones, dihydroxybenzone, oxybenzone, sulisobenzone); (c) moisturizers (e.g., emollients, Jojoba esters); (d) hydroxyacids (e.g., citric acid, malic acid, lactic acid); (e) depigmenting agents (e.g., hydroquinone, ascorbic acid, kojic acid, glabridin); (f) exfoliants (e.g., salicylic acid, lactic acid, glycolic acid); (g) antioxidants (e.g., α-lipoic acid, vitamins A, C, E, niacinamide, *N*-acetyl-glucosamine, α-tocopherol, lactobenzoic acid, ubiquinone, polyphenols); (h) proteins/peptides (e.g., pentapeptides-KTTKS); and (i) growth factors.

Classes of Cosmeceuticals

a. Skin cosmeceutical product—Antiaging creams, moisturizers, facial products, and lotions;
b. Hair cosmeceutical product—Gel and creams, hair colorants and dyes, shampoos, growth stimulators, and conditioners; and
c. Others—Lipstick, nail polish, toothpaste, and powders.

a. Skin cosmeceuticals

These cosmeceuticals are the cosmetic products that have medicinal or drug-like benefits are able to affect the biological functioning of skin owing to the type of functional ingredients they contain. These are skin care products that go beyond coloring and adorning the skin. Such products improve the functioning/texture of the skin by encouraging collagen growth by combating harmful effects of free radicals, thus maintaining keratin structure in good condition and making the skin healthier. OLAY vitamin line, which includes vitamins A, C, D, E, selenium, and lycopene, pycnogenol plus zinc and copper, is a well-known skin care line. The treatment of aging skin with a cream containing a hormone such as estrogen results in a fresh appearance with a rejuvenating effect. Kuno and Matsumoto (2004) had patented an external agent for the skin comprising an extract prepared from olive plants as a skin beautifying component, in particular, as an antiaging component for the skin, and/or a whitening component. Dry emollient preparation containing monounsaturated Jojoba esters was used for cosmeceutical purpose. Martin (2004) utilized plant extract of genus chrysanthemum in a cosmetic composition for stimulating skin and/or hair pigmentation (Preetha and Karthika 2009).

Commonly Used Skin Cosmeceuticals

(i) Hydroxy acid: Hydroxy acid also referred to as fruit acids; they are a common ingredient found in many cosmeceutical products. Examples include citric acid, malic acid, and lactic acid. AHAs improve skin texture and reduce the signs of aging by promoting cell seeding in the outer layers of the epidermis and by restoring hydration. AHAs also reduce the calcium ion concentration in the epidermis and the resulting reduction of the calcium ion levels tends to promote cell growth and slow cell differentiation, thus giving rise to younger looking.

(ii) Botanicals: Botanicals comprise the largest category of cosmeceutical additives found in the market place today. Some botanicals that may benefit the skin include green tea extract, ferulic acid, and grape seed extract.
Ferulic acid: This compound, which is derived from plants, is considered to be a potent antioxidant and has been shown to provide photo protection to skin. Furthermore, when ferulic acid is combined with vitamins C and E, the product has been shown to provide substantial UV protection for human skin. Moreover, Murray et al. (2008) reported that because its mechanism of action is different from sunscreens, ferulic acid could be expected to supplement the sun protection provided by sunscreens.
Grape seed extract: This botanical has been established as a potent antioxidant and has been shown to speed wound contraction and closure. Topical application of grape seed extract has also been shown to enhance the sun protection factor in humans.

(iii) Depigmenting agent: Skin-lightening agents added to product formulations have become increasingly popular, and such products are in demand. Common depigmenting ingredients include hydroquinone, ascorbic acid (vitamin C), kojic acid, and licorice extract (glabridin).
Hydroquinone: Hydroquinone has been the popular agent of choice for skin lightening. The US FDA has proposed concentrations between 1.5 and 2% in skin lighteners. A recent study suggests that this concern has been based mainly on studies with animal models utilizing long-term exposure at high dosages which are carcinogenic. Routine topical application may pose no greater risk than that from levels present in common foods.

(iv) Exfoliants: Exfoliants promote skin turnover by removing adherent cells in the stratum corneum. Common exfoliants found in cosmeceutical preparations include salicylic acid (SA), lactic acid, and glycolic acid. There are concerns that repeated use of SA and AHAs could cause the dermis and epidermis to be more vulnerable to penetration by UV radiation.

(v) Moisturizers: Moisturizers restore water content to the epidermis and provide a soothing protective film. They improve the appearance and tactile properties of dry and aging skin, restore the normal barrier function of the skin, and reduce the release of inflammatory cytokines. Moisturizers comprise an important therapeutic component in the management of various skin conditions (e.g., eczema, psoriasis, pruritus, and aged skin).

(vi) Topical peptides: These are regarded as cellular messengers that are formed from amino acids and are designed to mimic peptide fragments with endogenous biologic activity. These pentapeptides (e.g., KTTKS) are comprised of a subfragment of type I collagen propeptide and play a role in signaling fibroblasts to produce collagen in the skin, which can improve the appearance of wrinkles.

(vii) Retinoids: They are among the most common ingredients found in cosmeceuticals. In fact, they are the most studied and have the most data behind them. They consist of natural and synthetic derivatives of vitamin A that reduce hyperpigmentation and inhibit enzymes from breaking down collagen.

(viii) Sunscreen: Sunscreens are the single most important cosmeceutical, because they protect skin against solar radiation, which is the most important damaging environmental agent. As a result, they help to prevent the signs of aging. To be effective, sunscreens should provide broad-spectrum coverage that includes both UVA and UVB blocking agents to inhibit photoaging and be part of a daily skin care regimen. Sunscreens contain active ingredients that act as ultraviolet filters.

(ix) Antioxidants: Antioxidants reduce free radical damage, thereby preventing impairment at the cellular level. They inhibit inflammation, which leads to collagen depletion, and they offer protection against photodamage and skin cancer. Common antioxidants include alpha-lipoic acid (ALA), L-ascorbic acid (vitamin C), niacinamide (vitamin B3), *N*-acetyl-glucosamine (NAG), α-tocopherol, and ubiquinone.

Cosmetic Versus Drug

The term cosmetic refers to a preparation designed to enhance the body superficially to hide a real comprehended deficiency or flaw, by direct application. This application is considered to be decorative, lacking in depth or significance, as opposed to a response to a medical requirement. The definition of a drug is more complex. Generally, a drug is a chemical substance which, when absorbed into a living organism, alters normal function. The pharmacology definition of a drug will apply—'a chemical substance used in the treatment, cure, prevention or diagnosis of disease or used to otherwise enhance physical or mental well-being, for a limited duration or indefinite period of time.' Individual governments regulate the availability or drugs to the public as:

(i) Over-the-counter (OTC) medication is available from pharmacies;

(ii) Behind-the-counter medication (BTC) must be dispensed by pharmacist, but does not require the authority of a doctor; and finally

(iii) Prescription-only medicine (POM) can only be prescribed by a licensed medical professional.

There are also numerous bodies that regulate the drugs present in the market including:

(a) The Medicines and Healthcare products Regulatory Agency (MHRA) is a government agency responsible for ensuring that medicines and medical devices work and are acceptably safe. They are responsible for public information as well the investigation and handling of complaints and patient feedback.
(b) The National Biological Standards Board (NBSB) is a non-departmental public body, established in 1975 by Act of Parliament. The board takes responsibility for safeguarding and advancing public health by assuring the following.

Regulations
There is no regulatory category for cosmeceuticals. In fact, FDA does not recognize the word as an official product type, but it regulates cosmetics under the Federal Food, Drug and Cosmetics Act (FDCA). The regulations of cosmeceuticals have not been harmonized between the USA, European, Asian, and other countries yet.

5.4 Proteins, Peptides, and Enzymes as Drugs

Peptides and proteins are complex molecules of naturally occurring 20 different α-amino acid monomers, which joined with each other by peptide bonds. Proteins consist of one or more peptide chains, and peptides are small chains of amino acid monomers and distinguished from proteins by their size (peptide contains <50 monomer units and molecular weight <5 kD, while a protein possesses ≥ 50 amino acids and its molecular weight lies >5 kD). Peptides allow the development of antibodies of a very specific region of a protein, useful for the identification of proteins of interest based on peptide masses and sequence, and peptides are used in clinical research to examine the inhibition of different diseases including cancer. Different fermentation, purification processes, and recombination technology produced potential protein drugs at acceptable cost which can be useful in various diseases through various routes like oral, transdermal, nasal, pulmonary, ocular, buccal, and rectal. Availability and therapeutic application of proteins and peptides as drugs will replace many existing organic-based pharmaceuticals.

Ailments that might be treated with this type of therapeutics include autoimmune diseases, cancer, mental disorder, hypertension, and certain cardiovascular and metabolic diseases. Recombinant technology has allowed the production of many potential protein drugs at an acceptable cost, allowing the treatment of severe, chronic and life-threatening diseases, such as diabetes, rheumatoid arthritis, and hepatitis. The first genetically engineered drug was insulin. The second recombinant enzyme drug was Activase1 (alteplase, recombinant human tissue plasminogen activator). It was approved by the Food and Drug Administration (FDA) for the treatment of heart attacks caused by the blockage of a coronary artery by a clot.

Currently, over 160 protein drugs are available on the world market, and several hundreds more are in clinical trials. The total protein drug market already exceeds 30 billion and is expected to rise by at least 10% a year. One of the biggest opportunity areas in the Protein Therapeutics Market will be in the field of Biogenerics, which is expected to create a multi-billion dollar market in future.

Many protein pharmaceuticals are available for treating rheumatoid arthritis, coronary artery thrombosis, multiple sclerosis, and chronic lymphocytic leukemia (Sheremata et al. 2005; Lequerré et al. 2008; Zhou et al. 2009). Some isolated proteins have been approved by the Food and Drug Administration (FDA) of the USA for clinical use or clinical trials. Some protein pharmaceuticals from Chinese medicine have been developed to treat cardiovascular diseases, genetic diseases, and cancer. Luteinizing hormone—releasing hormone (LHRH) agonist (also called LHRH analog or GnRH antagonist)—is a naturally occurring decapeptide hormone with a molecular weight of 1.182 kD. It is used in the treatment of prostate carcinoma. Insulin is a protein molecule, with a molecular weight of 6 kD. It is used in the treatment of diabetes. Vasopressin is a nonapeptide with a molecular weight of 1.084 kD. It is used as an antidiuretic hormone.

Examples of ten common natural peptides (with the number of their amino acid residues) include: glutathione (a tripeptide) is a common non-ribosomal peptide and a component of the antioxidant defenses of most aerobic organisms, present in most living cells, and stimulates tissue growth; TRH (a tripeptide) is hypothalamic neurohormone and governs release of thyrotropin; angiotensin II (octapeptide) is a pressor agent and acts on the adrenal gland; bradykinin (nonapeptide) is hypotensive vasodilator and acts on smooth muscle; oxytocin (nonapeptide) is uterus-contracting hormone and also stimulates lactation; somatostatin (consisting of 14 amino acid residues) inhibits growth hormone release and used to treat ulcers; endothelin (consisting of 21 amino acid residues) is potent vasoconstrictor and structurally similar to some snake venoms; melittin (consisting of 26 amino acid residues) is honey bee venom and used to treat rheumatism; glucagon (consisting of 29 amino acid residues) is hyperglycemic factor and used as an antidiabetic; and insulin (consisting of 51 amino acid residues) is pancreatic hormone and used in treatment of diabetes.

Bioactive proteins and peptides with various pharmacological properties have been successfully isolated from different Chinese herbs including (i) medicinal fungi such as *Cordyceps militaris*—lectin designated as CML (31 kDa), Ling Zhi-8 (12.4 kDa protein); *Ganoderma* spp.—lectin (a 18-kDa protein); *Poria cocos*—*P. cocos* immunomodulatory protein (35.6 kDa) (PCP); (ii) medicinal plants such as *Viola tricolor*—cyclotides; *Momordica cochinchinensis* seeds—cochinin B (28 kDa ribosome inactivating protein), MCoCC-1 (a 33 amino acid long peptide), chymotrypsin inhibitor designated as MCoCI (7.5 kDa); *Viscum album*—lectin designated as CM-1 (55 kDa) and as ACML-55; the seeds of *Senna obtusifolia*—novel protein (19.7 kDa); *Narcissus tazetta* var. *chinenesis*—*Narcissus tazetta* lectin (26 kDa); *Smilax glabra* rhizomes—smilaxin (30 kDa); *Ginkgo biloba* seeds—ginkbilobin (13 kDa); *Dioscorea batata*—dioscorin (32 kDa); *Trichosanthes kirilowii*—trichosanthin (247 amino acid long peptide); and (iii) medicinal animals

such as *Hirudo* spp. (Leeches)—hirudin; *Eisenia fetida* (earthworm)—earthworm fibrinolytic enzyme—and *Mesobuthus martensii*—antiepilepsy protein (8.3 kDa). These therapeutic proteins, peptides, and enzymes, in vitro and/or in vivo experiments, were found active against different types of cancer, oxidative stress, cholesterol biosynthesis, and some showed antiviral, antibacterial, antifungal, anticoagulant, antiepileptic, anti-HIV as well as immunomodulatory (Byers and Baldwin 1991; Rydel et al. 1991; Wang and Ng 2000; Tsoi et al. 2005; Chu and Ng 2006; Ricotti and Delanty 2006; Chen et al. 2007; Li et al. 2008; Ma et al. 2008; Ooi et al. 2010; Tang et al. 2010).

Important features that distinguish features of enzymes as drugs from all other drugs are (i) their great target binding affinity and specificity and (ii) catalytic properties, and these characteristics have resulted in the development of many enzyme drugs for a wide range of disorders (Vellard 2003). Proteolytic enzymes digest protein by aiding in the digestion process breaking it down into amino acids. They can be taken as a supplement, but better yet, they can be found naturally in certain foods. A great example is papaya, which contains the proteolytic enzyme papain, a popular meat tenderizer. Papain found in papayas may be very helpful for the prevention of atherosclerosis and diabetic heart disease.

Proteolytic enzymes are also known as proteases. The three main proteases are pepsin, trypsin, and chymotrypsin. The protease enzyme breaks down protein found in meats, poultry, fish, nuts, eggs, and cheese and may be helpful for people with food allergies or those who have difficulty digesting protein. Some manufacturers derive their enzymes from animal sources. For example, supplements that contain trypsin or chymotrypsin are extracted from livestock, while supplements that contain papain or bromelain come from plant sources.

Proteolytic enzymes modulate the inflammatory process by a variety of mechanisms, including reducing the swelling of mucous membranes, decreasing capillary permeability, and dissolving blood clot-forming fibrin deposits and micro thrombi. By reducing the viscosity (thickness) of the blood, proteolytic enzymes improve circulation. This consequently increases the supply of oxygen and nutrients to and the transport of harmful waste products away from traumatized tissue. Proteolytic enzymes also help break down plasma proteins and cellular debris at the site of an injury into smaller fragments. This greatly facilitates their passage through the lymphatic system, resulting in more rapid resolution of swelling, with the consequent relief of pain and discomfort in the bones and joints affected. These enzymes can help athletes recover faster from hard workouts and races.

Vellard (2003) mentioned ten FDA-approved enzymes designated as orphan drugs in the USA. They are (i) Adagen (pegademase bovine), for enzyme replacement therapy for ADA in patients with severe combined immunodeficiency disease (SCID); (ii) Ceredase (alglucerase injection), for enzyme replacement therapy in patients with Gaucher's disease type I; (iii) Pulmozyme (dornase alpha), enzyme to reduce mucous viscosity and enable the clearance of airway secretions in patients with cystic fibrosis (CF); (iv) Cerezyme (imiglucerase), for enzyme replacement therapy in patients with types I, II, and III Gaucher's disease; (v) Oncaspar (pegaspargase), enzyme for treatment of acute lymphocytic leukemia;

(vi) Sucraid (sacrosidase), enzyme for treatment of congenital sucrase-isomaltase deficiency; (vii) Elitek (rasburicase), enzyme for treatment of malignancy-associated or chemotherapy-induced hyperuricemia; (viii) Fabrazyme (agalsidase beta), enzyme for treatment of Fabry's disease; (ix) Aldurazyme (laronidase), enzyme for treatment of patients with MPS I; and (x) Replagal (α-galactosidase A), enzyme for long-term enzyme replacement therapy for the treatment of Fabry's disease.

5.5 Pharmacological and Synergistic Activities of Herbal Products

Compared to herbal medicines, conventional drugs are relatively straightforward to investigate because they are of single chemical entities. They can be studied in strict isolation, and there is nothing in the drug's dose form which can interfere to any significant extent with its pharmacological behavior. By the time it reaches the market, the pharmacology of virtually every drug has been exhaustively researched; the physiological response to it can generally be predicted with considerable accuracy and precisely standardized.

Compared to modern medicines of single chemical entities, herbal medicines are very different and usually consist of many compounds, each with separate, varying, and distinct pharmacological activities. From the pharmacological point of view, the situation is unbelievably complex; each component has a different pharmacological activity, but there is invariably an interaction between the different components of the herbal medicine; one component affects other pharmacologically active agents in synergistic way, which means that the effect of combined treatment is more than the sum of each component's individual effects (i.e., certain components in a plant extract can improve the therapeutic effect of active agents). In the patient, one herb can enhance the effect of another given at the same time (i.e., the combined effect of a number of herbal components is actually greater than the sum of each of the individual components). Goldenseal, used for skin infections, contains alkaloid berberine, which in isolation has only weak antibacterial activity. This is potentiated by other substances in the plant, which are inactive themselves. When the herbal ginger extract is used the antiulcer effect is sixty-six times more effective than the active agent, zingiberene, when isolated and used alone, the bioavailability of vitamin C present in many plants is improved when bioflavonoids like rutin are present (Mabey 1988).

The meaning of synergy has now been broadened and extended to include other related concepts. Synergy is now used to describe the effect of one herb in improving the effect of another. For example, use of the laxative senna can lead to stomach cramps in some people. If ginger is taken simultaneously, then these cramps are avoided, or at least minimized. In the practice, herbal medicines are prescribed in a combination of several herbs with the desired outcome of improving

patient benefit. A further meaning of synergy relates to the simultaneous use of herbs with other contributors to health care (combining herbal therapy with adjustment to lifestyle). For example, the herbal therapy for joint pains will be much effective when combined with a specific diet or mild form of exercise. An asthmatic patient will benefit far more when herbal therapy is combined with breathing exercises, chest massage, and improved sleep hygiene.

The mechanism of synergistic effect cannot yet be satisfactorily explained. Based on the nature of the interaction between the components of herbal drugs, two broad types of synergy can be distinguished such as (i) pharmacodynamic interaction (how a drug affects an organism, biochemical, and physiologic effects of drugs on organism) and (ii) pharmacokinetic interaction (how the organism affects the drug or the way in which drugs move through the body during absorption, distribution, metabolism, and excretion of drugs). (i) Pharmacodynamic synergy results from two drugs directed at a similar receptor target or physiological system. For example, combinations of allosteric modifiers at the gamma-aminobutyric acid A (GABAA) receptor create potent synergistic interactions. (ii) Pharmacokinetic synergy results from the processes of drug absorption, distribution, metabolism, or elimination. For example, combined administration of drugs which compete for albumin binding sites on blood cell membrane will elevate the free drug concentrations and thus potentiate their actions (one herbal component may improve absorption and bioavailability of a second). When two psychoactive herbs such as kava and valerian are given to a patient with anxiety, the response is likely to be markedly greater than the sum of the two given separately.

St. John's wort (*Hypericum perforatum*), kava kava (*Piper methysticum*), and valerian (*Valeriana officinalis*) are examples that illustrate synergistic actions (Spinella 2002) and shown in Table 5.13.

Table 5.13 Summary of synergistic mechanisms

Herbal source and contents	Type of synergy	
	Pharmacodynamic	Pharmacokinetic
St. John's Wort contains naphtodianthrones, flavonoids, phloroglucinols, phenolic acids, xanthones, and terpenes	Monoamine reuptake inhibition; MAO inhibition; COMT inhibition	Procyanidin increases bioavailability of hypericin
Kava kava contains kava lactones, principally kavain, dihydrokavain, yangonin, dimethoxyyangonin, methysticin, and dihydromethysticin	GABAA facilitation; Na^+ and Ca^{2+} channel inhibition; MAO inhibition; reuptake inhibition of NE	Kavalactones increase each other's bioavailability
Valerian contains valeranone, dihydrovaltrate, valeric acid, isovaleric acid (monoterpenes and sesquiterpenes)	Multiple GABA mechanisms	Not yet investigated

MAO Monoamine oxidase, *COMT* Catechol-*o*-methyltransferase, *GABAA* Gamma-aminobutyric acid A, *NE* Norepinephrine
[naphtodianthrones (hypericin, protohypericin, pseudohypericin, and protopseudohypericin)]

The above table illustrates multiple examples of pharmacodynamic and pharmacokinetic synergy at work in psychoactive herbal medicines. St. John's wort shows evidence of pharmacodynamic synergy through monoamine neurotransmitter systems, preventing neurotransmitter breakdown and blocking reuptake. Pharmacokinetic synergy is evident in St. John's wort since procyanidin (flavonoids) increases the bioavailability of the naphtodianthrones (hypericin). Kava kava's effects on GABA and voltage-gated ion channels (and possible monoamine systems) create pharmacodynamic synergy. Kava kava also shows evidence of pharmacokinetic synergy since the administration of combined kava lactones increases brain bioavailability of each, compared to individual administration. Valerian shows evidence of pharmacodynamic synergy since multiple constituents of the herb are acting on GABAergic systems, both pre- and post-synaptically. Pharmacokinetic synergy in valerian is possible, but has not yet been investigated.

The above examples of synergy are directly relevant to the therapeutic benefits of these herbal medicines. The synergistic effects of St. John's wort likely enhance its effects on monoamine neurotransmitter systems, the predominant mechanism of most antidepressant drugs. The synergistic interactions of kava kava occur through GABA, voltage-gated ion channel, and monoamine systems. All of these mechanisms help account for kava kava's demonstrated antianxiety effects. The synergistic effects of valerian's constituents on GABA transmission would explain its demonstrated effects on sleep.

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Chapter 6
Pharmacognostical Botany: Classification of Medicinal and Aromatic Plants (MAPs), Botanical Taxonomy, Morphology, and Anatomy of Drug Plants

Abstract Diverse plant species of the earth constitute the fundamental source of crude drugs and the diversified botanical species comprising of non-seed and seed plants, for the convenience of study, may be classified following artificial, natural, or phylogenetic system. None but the phylogenetic system put emphasis on the evolutionary relationship among different taxa of plants (e.g., Engler and Prantl, Bessey, Hutchinson, Takhtasan, Cronquists systems). Linnaeus artificial system is of little importance today, but his binomial system of nomenclature of organisms is now widely practiced. The various taxa or ranks used in plant classification following ICBN in ascending hierarchy are Species, Genus, Family, Order, Class, Subdivision, Division, and Kingdom. The naming of plants and understanding of the species' relationship to other species is essential for botanists, pharmacognosists, phytochemists, and other professionals working in the field of plant science. Taxonomic or botanical identity of medicinal plants is a fundamental step in the scientific study for their effective therapeutic use as well as forms the basis of correct identification and authentication of crude drugs from adulterants. Documentation requires an accurately identified vouchered plant sample of a recognized herbarium. Secondary metabolites and pigments (e.g., alkaloids, phenolics, terpenes, anthocyanins, carotenoids) constitute the active therapeutic principles of crude drugs (e.g., inulin of dahlia root, quinine of cinchona bark, morphine and codeine of poppy latex, and digoxin of foxglove). Similarly, therapeutically important other metabolites like agar, alginic acid, floridean starch, iodine, potash are derived from algae; ergoline alkaloids, lysergic acid derivatives, vitamin B complex and different antibiotics from fungi; and essential oils (e.g., alphapinene and borneol), balsams, flavonoids, condensed tannins, lignans, etc., are widely present in the members of Pinaceae. Important plant families of angiosperms to which a large number of medicinal plants belong are Apiaceae, Apocinaceae, Asteraceae, Boraginaceae, Brassicaceae, Caryophyllaceae, Cesalpinaceae, Cucurbitaceae, Fabaceae, Lamiaceae, Malvaceae, Mimosaceae, Papaveraceae, Phytolaccaceae, Ranunculaceae, Roseaceae, Rutaceae, Solanaceae, Scrophulariceae and Verbenaceae of dicot and Liliaceae, Orchidaceae, and Zingiberaceae of monocot. Systematics is an important tool in pharmacognostical practice and may be helpful to guess the probable presence of secondary metabolites in different taxa;

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for example, many members of Apiceae contain essential oils, presence of highly aromatic compounds in the members of Lamiaceae, alkaloids in Solanaceae, Papaveraceae and tannins in members of Sapindaceae. Structural description of a drug plant at morphological (macroscopic) and anatomical (microscopic) levels as used in the pharmacopoeial texts of crude drugs is important for its botanical identity, quality of herbal preparation, and pharmacognostical standardization. Roots, stems, and leaves as well as flowers and fruits are the basic morphological organs of higher plants. Modification of some of these organs are also known, e.g., stem modified into underground (rhizome, tuber, bulb, corm, etc.), subaerial (runner, stolon, offset, sucker, etc.), and aerial (tendril, spine, phylloclade, cladode, bulbil) stems to take over different functions. Shape, size, and forms as well as color, texture, fracture aspects, and characteristics of the cut surface of these major organs and associated other minor structures are also taken into consideration. Morphological identity is very often needed to be supplemented by anatomical characters because many different closely related plants look similar in their external appearance and comminuted drugs loss their morphological identity. The basic unit of plant body is a cell, and organized cells develop tissue and specific organs like root, stem, leaf, flower, fruit, seed of the organized drugs. A clear understanding of the structure, organization, and contents of these cells and tissues is important for meaningful study and correct botanical identification of crude drugs. Cells vary in size (1–100 μm) and shape (spherical, oval, polygonal, rectangular, or elongated). Cell components are divisible into cell wall, protoplasm, and vacuole. A cell wall may contain lignin, cutin, suberin, mucilage, etc., in addition to cellulose. Cells with lignified walls are dead and characteristics of the mechanical and vascular tissues such as tracheids, fibers, sclereids, and vessels. Plasma membrane, cytoplasm, and nucleus constitute the protoplasm. Cytoplasm is a translucent mass of colloidal substances, composed of water, protein, carbohydrate, lipoids, and various inorganic substances. The waste or ergastic products of metabolism occur as cell contents in a number of plant drugs include solid substances (e.g., calcium oxalate and calcium carbonate crystals, silica), and substances in solution in the cell sap (e.g., alkaloids, glycosides, volatile oils, resins, tannins, gums, mucilage). Calcium oxalate crystals are of considerable diagnostic importance of plant drugs (e.g., prisms of calcium oxalate occur in Senna, Liquorice, Cascara, Rauvolfia); raphides (e.g., bundles of needles in Coco-yam, Squill); single acicular crystals (in Cinnamon, Gentian, Ipecacuanha, microsphenoidal, etc.), or sandy crystals (e.g., in Belladonna). Calcium oxalate crystals are also useful in distinguishing between the drugs of the same family. Calcium oxalate crystals are also useful in the detection of adulterants (e.g., presence of Phytolacca leaves in Belladonna samples can be detected by the acicular crystals of Phytolacca). These crystals are found embedded or incrusted in the cell walls of certain plants (e.g., calcium carbonate crystals, cystoliths, occur in many plants of the families: Urticaceae, Moraceae, Cannabinaceae, Acanthaceae, and also in Combretaceae and Boraginaceae). The occurrence of cystolith hairs is an important criterion for the identification of marijuana leaf fragments. Alkaloids and glycosides are important therapeutically active chemical substances, which remain in solution in the cell sap

of many plant drugs. Their presence can only be detected by Dragendorff or Mayer's reagent for alkaloids and Borntrager's reagent for anthraquinone glycosides. The internal structural knowledge is applicable for the identification of organized crude drugs, while the botanical identity of unorganized drugs should be determined by chemical analysis.

Keywords Taxonomic identity · ICBN · Morphological characteristics · Anatomical characteristics · Ergastic substances

6.1 Classification of Medicinal and Aromatic Plants (MAPs)

Medicinal (including aromatic) herbs or plants may classified in various ways such as on the basis of their (i) use (e.g., medicinal herbs, culinary herbs, aromatic herbs, ornamental herbs), (ii) active constituents they contain (e.g., bitter compounds, tannins, volatile oils), (iii) their period of life, and (iv) their botanical taxonomy.

Medicinal herbs have curative powers and are used in making medicines because of their healing properties. Culinary herbs are probably the mostly used as cooking herbs because of their strong flavors like mint, parsley, basil. Aromatic herbs have some common uses because of their pleasant smelling flowers or foliage. Oils from aromatic herbs can be used to produce perfumes, toilet water, and various scents, e.g., mint, rosemary, basil, etc. Ornamental herbs are used for decoration because they have brightly colored flowers and foliage like lavender, chives, etc.

Aromatic herbs bear pleasant odor, and many of these herbs are used extensively both therapeutically and as flavorings and perfumes. Aromatic herbs may be stimulants and nervines. Stimulant herbs increase energy and activities of the body, or its parts or organs, and most often affect the respiratory, digestive, and circulatory systems, e.g., fennel, ginger, garlic, lemon grass. Nerving herbs are often used to heal and soothe the nervous system, and often affect the respiratory, digestive, and circulatory systems as well. They are often used in teas or in encapsulated form, e.g., ginger, catnip.

Five major categories of active constituents such as volatile oils (aromatic), tannins (astringents), compounds like phenols, saponins, alkaloids (bitter), polysaccharide substances (mucilaginous), and food stuffs (nutritive) are present in herbs, and accordingly, the herbs may be classified into five groups (aromatic, astringent, bitter, mucilaginous, and nutritive).

Astringent herbs have tannins to precipitate proteins, and this tightens, contracts, or tones living tissue, and helps to halt discharges. They affect the digestive, urinary, and circulatory systems, and large doses are toxic to the liver. They are analgesic, antiseptic, antiabortive, astringent, emmenagogue, hemostatic, and styptic, e.g., peppermint, red raspberry.

Bitter herbs contain bitter principles like phenols, phenol glycosides, alkaloids, saponins, and they are subdivided into laxative herbs, diuretic herbs, saponin-containing herbs, and alkaloid-containing herbs. Laxative bitter herbs include alterative, ant catarrhal, antipyretic, cholagogue, purgative, hypotonic, sialagogue, vermifuge, and blood purifier, e.g., aloe, cascara, liquorice, pumpkin, senna, yellow dock, yucca, barberry, gentian, safflowers, and golden seal. Diuretic herbs induce loss of fluid from the body through the urinary system. The fluids released help cleanse the vascular system, kidneys, and liver. They are alterative, antibiotic, ant catarrhal, antipyretic, and antiseptic, lithotripter, and blood purifier in nature, e.g., asparagus, blessed thistle, burdock, butcher's broom, buchu, chaparral, chickweed, corn silk, dandelion, dog grass, grapevine, and parsley. Saponin-containing herbs are known for their ability to produce frothing or foaming in solution with water. They emulsify fat soluble molecules in the digestive tract, and their most important property is to enhance the body's ability to absorb other active compounds.

Saponins have the ability to effectively dissolve the cell membranes of red blood cells and disrupt them. They are alterative, ant catarrhal, antispasmodic, and aphrodisiac, emmenagogue, cardiac stimulant, and increased longevity in nature, e.g., yam root, schizandra, black cohosh, blue cohosh, devil's claw, liquorice, alfalfa, yucca, ginseng, and gotu kola.

Mucilaginous property of herbs is due to polysaccharide content that produces a slippery and mild sweet taste in water. Most mucilaginous substances are not broken down by the human digestive system; they absorb toxins from the bowel and give bulk to the stool. Mucilaginous herbs are most effective topically as poultices and knitting agents and are also used topically in the digestive tract. They eliminate the toxins from the intestinal system, help in regulating it, and reduce the bowel transit time. When used as lozenges or extracts, they have a demulcent action on the throat. They are antibiotic, antacid, demulcent, emollient, vulnerary, and detoxifier in nature, e.g., althea, aloe, burdock, comfrey, dandelion, Echinacea, fenugreek, kelp, psylium slippery elm, dulse, glucomannan from Konjak root, Irish moss, and mullein.

Nutritive herbs add nutritive value to the diet. They are true foods and provide some medicinal effects as fibber, mucilage, and diuretic action. But most importantly they provide the nutrition of protein, carbohydrates, and fats, plus the vitamins and minerals that are necessary for adequate nutrition, e.g., rosehips, acerola, apple, asparagus, banana, barley grass, bee pollen, bilberry, broccoli, cabbage, carrot, cauliflower, grapefruit, hibiscus, lemon, oat straw, onion, orange, papaya, pineapple, red clover, spirulina, stevia, and wheat germ.

According to their longevity or life cycle, medicinal plants or herbs are classified as annuals, biennials, and perennials. Annuals complete their life cycle in one season or year and then die, biennials live for two years or seasons, and bloom in the second season and perennials live over winter and bloom in each season.

Annual herbs include Anise, Basil, Borage, Calendula, Chamomile, Chervil, Coriander, Dill, Fennel, Parsley, Saffron, Savory; biennial herbs include Caraway seeds, Prime rose, Mullein, Teasel; and perennial herbs include Alfalfa, Aloe Vera,

Angelica, Bay leaves, Lavender, Lemon Balm, Mints (Spearmint, peppermint, apple mint, orange mint), Rosemary, Sage, Tarragon, Thyme, Watercress.

MAPs may also be classified on the basis of their habit (herb, shrub, liners, climbers, trees, etc.), mode of nutrition (autotrophs, heterotrophs, symbiotic, etc.) as well as habitat (hydrophytes, mesophytes, xerophytes, lithophytes, epiphytes, heliophytes, sciophytes, halophytes, etc.). Distribution of medicinal plants by habitats may be approximately 32% herbs, 20% shrubs, 33% trees, 12% climbers, and 3% others.

6.2 Botanical Classification or Taxonomy of MAPs and Their Families

All medicinal MAPs produce chemical compounds like secondary metabolites and pigments (e.g., alkaloids, phenolics, terpenes, anthocyanins, carotenoids). These chemical compounds constitute the active therapeutic principles of crude drugs, e.g., inulin of the roots of dahlias, quinine of the bark of cinchona, morphine and codeine of the latex of poppy, and digoxin of the foxglove. Botanical or taxonomic identity of medicinal plants is necessary for their effective therapeutic use. Determination of botanical identity is a fundamental step in the scientific study of medicinal plants. Plant classification, taxonomy, phylogeny, and systematics are interrelated terms where classification describes the procedure of arranging of organisms into groups (i.e., putting things in classes), taxonomy is concerned with the study of principles and procedures of classification (i.e., giving names to things in a way that reflects their classification), phylogeny (i.e., true tree of life) is the evolutionary hierarchical structure by which every life-form is related to every other life-form and systematics (i.e., classification of plants and animals according to their phylogeny) deals with the study of comparative and evolutionary relationships of plants, based on their anatomy, physiology, and biochemistry. Phylogenetic relationships are visualized as evolutionary tree that has two components (a) branching order (group relationships) and (b) branch length (extent of evolution). Systematics is an important tool in pharmacognostical practice, and research and knowledge about the systematic position of a particular plant may be helpful to guess the probable presence of secondary metabolites in it, e.g., many members of Apiceae contain essential oils, highly aromatic compounds in the members of Lamiaceae, presence of alkaloids in Solanaceae, Papaveraceae and tannins in members of Sapindaceae. Members arise from Liliaceus ancestors (e.g., Liliaceae, Juncaceae, Cyperaceae, Gramineae) contain flavonoids in the leaf. Ten families of Caryophyllales (e.g., Aizoaceae, Amaranthaceae, Basellaceae, Cartophyllaceae, Chenopodiaceae, Didieraceae, Molluginaceae, Nyctaginaceae, Phytolaccaceae, and Portulaceae) contain betalains (a nitrogenous anthocyanins consisting of red to violet betacyanins and yellow betaxanthins). Terpenoids are extensively present in the members of Apiaceae, Rutaceae, and gymnosperms. Many taxa of Araceae, Gramineae, Juncaceae, Juncaginaceae, and Scheuchzeriaceae are cyanogenic.

Pharmacognosy is involved in the study of medicinal products derived from natural sources like plants, animals, insects, microbes, minerals. The earth is endowed with rich biodiversity, and plant diversity is composed of >500,000 botanical species comprising of algae, fungi, lichens, liverworts, mosses, ferns, conifers, and flowering plants. Classification is a prerequisite to study the various aspects of plant diversity. Following the International Code of Botanical Nomenclature (Voss 1983), the various taxa (i.e., ranks) used in classification in ascending hierarchy with their ending and examples (within parenthesis) are: Species (grandiflora L.), Genus (a, e.g., Magnolia), Family (ceae, e.g., Magnoliaceae), Order (ales, e.g., Magnoliales), Class (opsida, e.g., Magnoliopsida), Subdivision (phytina, e.g., Magnoliophytina), Division (phyta, e.g., Magnoliophyta), and Kingdom (Plantae).

Taxon is a taxonomic unit that is used to indicate any taxonomic rank (i.e., Species, Genus, Family). As per the binomial system of nomenclature published in Species Plantarum (1753) by the Swedish Botanist Carl von Linnaeus (1707–1778), a plant name consists of two parts, e.g., genus and species. The name *Atropa belladonna* L. includes (i) the genus, generic name, or generic epithet, (*Atropa*) and (ii) species or specific epithet (*belladonna*) followed by the authority, L., stands for the botanist Linnaeus who provided the first scientific description of the species and assigned the botanical name. The generic name is a noun and should be written with capital initial letter, while the specific epithet is often an adjective and should be written with small initial letter. The name of the species is incomplete if it is not followed by name or names of author or authors. In hand written or printed matter, the species name should be underlined or in italics (or bold face), respectively. The authority name is never be underlined or in italics. The common or vernaculars names are derived from words of local language and vary from place to place where as the scientific names are accepted all over the world. The naming of plants and understanding of the species' relationship to other species is essential for botanists, pharmacognosists, phytochemists, and other professionals working in the field of plant science. Taxonomic identity forms the basis of correct identification and authentication of the crude drug and lead compound. Documentation of medicinal plant research requires an accurately identified voucher plant sample that should be kept in recognized herbaria. Lack of vouchers, misspelled names, lack of author citations for binomials, and misapplied synonyms lead to confusion and a lack of reproducibility. Voucher specimens serve as permanent records of scientific investigations.

6.2.1 Systems of Plant Classification: Artificial, Natural, and Phylogenetic

Three types of classification of plants, viz. (i) artificial or mechanical, (ii) natural, and (iii) phylogenetic systems are known. For artificial or mechanical system, only

one or a few characters were used to group taxa, for natural system, many characters were used while in phylogenetic system, evolutionary relationship among taxa are considered in addition to all possible characters from morphology, anatomy, cytology, biochemistry, and physiology of the concerned group of plants. The systems of classification put forward during the period of (i) Theophrastus (370–285 BC) up to Linnaeus (1707–1778) are artificial or mechanical, (ii) AP de Candole (1778–1841), Bentham (1800–1884), and Hooker (1817–1911) and some other people put forward natural system while (iii) Engler (1844–1930) and Prantl (1849–1893), Bessey (1845–1915), Hutchinson (1884–1972), and more recently Takhtajan (1980), Cronquist (1981), Dahlgren (1981) and Thorne (1981, 1992) proposed the phylogenetic system of classification of higher plants.

Armen Takhtajan published his system of plant classification in several versions from the 1950s onward (2009). He divided the phyllum Magnoliophyta (Angiospermae) into two classes, e.g., (i) Magnoliopsida (dicotyledons) and (ii) Liliopsida (Monocotyledons). He further divided Magnoliopsida into 7 subclasses, 20 superorders and 71 orders, and Liliopsida into 3 subclasses, 8 superorders, and 21 orders and a total of 410 families in two classes of flowering plants (Takhtajan 1980). It is usually compared to the Cronquist system.

Arthuer Cronquist published a taxonomic classification system of flowering plants under the captions: An Integrated System of Classification of Flowering Plants (1981) and The Evolution and Classification of Flowering Plants (1968; 2nd ed., 1988). The phylogenetic system as laid out in *An Integrated System of Classification of Flowering Plants* by Cronquist (1981) places flowering plants (angiosperms) into two broad classes such as (i) Magnoliopsida (dicotyledons) and (ii) Liliopsida (monocotyledons). Magnoliopsida contains 6 subclasses, 64 orders, 321 families, about 9600 genera, and about 170,000 species, and Liliopsida contains 5 subclasses, 19 orders, and 65 families about 2700 genera; about 50,000–60,000 species.

6.2.2 *Plant Taxa: Species, Genus, Family, Order, Class, Subdivision, Division, and Kingdom*

During the time of Aristotle (384–322 BC), the living world was divided into two groups under plants and animals. Aristotle for the first time proposed the scientific classification of plants and animals on the basis of morphological characters. Carolus Linnaeus (1735) in his Systema Naturae distinguished two kingdoms of living things, e.g., Plantae and Animalia on the basis of nutrition and mobility. Haeckel (1866) proposed a three-kingdom system (Protista, Plantae, and Animalia), the third kingdom Protista included all the single-celled organisms. Copeland (1938) suggested a fourth kingdom, Monera, to include the prokaryotes like bacteria and blue-green algae. Whittaker (1969) proposed an elaborate five-kingdom classification, viz. Protista (the single-celled eukaryotes), Fungi (fungus and related

organisms), Plantae (the plants), Animalia (the animals), Monera (the prokaryotes) using the criteria like cell structure, thallus organization, mode of nutrition, reproduction, and phylogenetic relationships, and this system was widely used for three decades and remains popular today. Woese et al. (1977) further elaborated the five-kingdom system to six-kingdom system by dividing Monera (the prokaryotes) into the Eubacteria and Archeobacteria on the basis of rRNA studies. Woese et al. (1990), later, proposed three domains (e.g., Archaea, Eubacteria, and Eukaryota) system and 23 divisions to accommodate all organisms. However, this may not be the end since some scientists have proposed to divide the organisms into more kingdoms (as many as 8).

Now there are several classifications of life including the three-domain system (e.g., Archaea, Eubacteria, and Eukaryota domains) of Woese et al. (1990), the two-empire system (e.g., Prokaryota or Monera and Eukaryota empires) of Mayr (1998), the five-kingdom system (e.g., Monera, Protista, Fungi, Plantae, and Animalia) of Whittaker (1969), the six-kingdom system (e.g., Archaebacteria, Monera, Protista, Fungi, Plantae, and Animalia) of Woese et al. (1977). Overall, the majority of biologists accept the domain system, but a large minority uses the five-kingdom method. A small minority of scientists adds Archaea or Archaebacteria as a sixth kingdom but do not accept the domain method.

According to Art 3.1 of the International Code of Nomenclature (ICN) for algae, fungi, and flowering plants, the most important taxonomic ranks in descending order are: kingdom, division, class, order, family, genus, and species. Rank is the relative level of a taxon (a group of organisms) in a taxonomic hierarchy. The taxonomic hierarchies of two species, one from each of (i) monocotyledons (e.g., *Allium cepa* L.) and (ii) dicotyledones (*Coriandrum sativum* L.) are shown in Table 6.1.

A species is a group of individuals, characterized by morphologically and functionally similar members; able to inbreed freely and true to type; have 2n chromosomes in somatic cells and n chromosomes in reproductive cells. A genus is a collection of species bearing a close resemblance to each other in terms of morphological and reproductive characters. A genus may be named (i) in honor of a person, e.g., Theophrasta, Candollea, Kaempferia after Theophrustus, AP de Candolle, E. Kaempfer, respectively; (ii) may be descriptive with reference to some common characteristics of the species, e.g., Cercocarpus (coiled fruit),

Table 6.1 Different taxa of Plant Kingdom in descending order

Ranks of Taxa	Example (i)	Example (ii)
Kingdom	Plantae (plants)	Plantae (plants)
Division	Magnoliaphyta (angiosperms)	Magnoliaphyta (angiosperms)
Class	Liliopsida (monocotyledones)	Magnoliopsida (dicotyledones)
Order	Liliales	Apiales
Family	Liliaceae	Apiaceae
Genus	*Allium*	*Coriandrum*
Species	*Allium cepa* L.	*Coriandrum sativum* L.

Xanthoxylum (yellow wood); (iii) poetic or mythological origin, e.g., Theobroma (good's food); or of (iv) aboriginal name, e.g., Betula (birch), Quercus (oak). The specific epithets may be with plant parts (sepalum for sepals or folium for leaf), color (albus—white, roseus—rosy), geography (africanas—Africa, canadensis—Canada), size (giganteus—gigantic, pumilus—dwarf), habit (erectus—erect, repens—creeping), habitats (aquaticus—growing in water, terrestris—growing in dry soil) or it may be given in honor of a person. Common names would be both ambiguous and confusing, and would group together plants which bear similar names, but are not related to each other, e.g., Alexandrian Laurel (*Calophyllum inophyllum* L.), Bay Laurel (*Laurus nobilis* L.), Cherry Laurel (*Prunus laurocerasus* L.).

A genus may contain one species (e.g., Abroma) or several species (e.g., Euphorbia, Ficus, Hibiscus). Variations occur within a species, and these are accommodated in (i) subspecies (ssp.), a distinct variant often arising because of evolution of plant form geographic factors, (ii) varieties (var.), a variant with small differences in morphology, and (iii) form (forma), have very minor differences, e.g., leaf or fruit color.

Hybrid plants arising from the sexual crossing of distinct species within the same genera are called interspecific hybrids and are indicated by a multiplication sign, e.g., Lavandin plants: *Lavandula* x *intermedia* are sterile hybrids between *Lavandula angustifolia* Mill. and *Lavandula latifolia* Medic. Less commonly met are plants arising from sexual crossings between different genera (intergeneric hybrids). Grafting one plant onto another can also produce hybridized plant growing onwards from the grafting point: These are indicated by a + sign linking the two involved species.

A family is a group of genera having general structural resemblance in their floral organs. Family name ending in all cases should be–ceae. However, the following names, owing to long usage, are an exception to the rule: *Compositae* (*Asteraceae*; type, *Aster* L.); *Cruciferae* (*Brassicaceae*; type, *Brassica* L.); *Gramineae* (*Poaceae*; type, *Poa* L.); *Guttiferae* (*Clusiaceae*; type, *Clusia* L.); *Labiatae* (*Lamiaceae*; type, *Lamium* L.); *Leguminosae* (*Fabaceae*; type, *Faba* Mill. [=*Vicia* L.]); *Palmae* (*Arecaceae*; type, *Areca* L.); *Papilionaceae* (*Fabaceae*; type, *Faba* Mill.); *Umbelliferae* (*Apiaceae*; type, *Apium* L.). When the *Papilionaceae* are regarded as a family distinct from the remainder of the *Leguminosae*, the name *Papilionaceae* is conserved against *Leguminosae*.

Chemotypes (ct.) or chemovars are morphologically indistinguishable individuals (plant or microorganisms) but chemically characterized with distinct differences in the composition of the secondary metabolites and individuals of one chemotype may have vastly different chemical profiles. There, perhaps, happen insignificant genetic and epigenetic changes with little or no effect on morphology or anatomy but large changes in the chemical phenotype. Secondary metabolites of the chemotypes (ct.), especially the essential oil profile is considered important in many cases for their demarcation. Chemotypes are generally described by the most abundant chemical produced by the individual and the chemical ecologists and natural product chemists generally use the term in their works. *Thymus vulgaris* may be assigned to one of seven different chemotypes, depending on the dominant

component of the essential oil (thymol, carvacrol, linalool, geraniol, sabinene hydrate or thuyanol, α-terpineol, or eucalyptol) and may be indicated as *Thymus vulgaris* ct. thymol (red thyme), *Thymus vulgaris* ct. geraniol (sweet thyme), etc. Such an indication has no taxonomic standing (Keefover-Ring et al. 2009). Morphologically stable species like *Chamomilla recutita* shows marked differences in the production of secondary metabolites (e.g., essential oil). Four chemotypes of *Ocimum sanctum* such as a citral type, a eugenol type, a methyl chavicol type, and a chavibetonal type were described by Hegnauer (1966). There are several chemotypes of the *Rosmarinus officinalis* (e.g., ct. 1,8-cineole, borneol, camphor, limonene) producing rosemary essential oil depending on both the growing conditions and the country it is growing in and each with their own therapeutic properties. A bank of knowledge now exists for specific oil-bearing plants, and a large number of such plants are yet remained undiscovered.

6.2.3 *Taxonomic Divisions of the Plant Kingdom: Thallophyta, Bryophyta, Pteridophyta, Gymnospermophyta, and Magnoliophyta; Pharmacognostical Importance the Taxonomic Groups*

Plants are a major source of medicines used in traditional medicine for the treatment of many diseases (Ambasta 1986; Bako et al. 2005). There are about 500,000 species of land plants (angiosperms, gymnosperms, ferns, lycophytes, and bryophytes) in different parts of the world with their strong domination in diversity in the humid tropics, and about 2500 species of plants from different groups are used as a source of herbal medicine (Pei 2001; Corlett 2016). Medicinal plants may be found in all groups of plants under the kingdom Plantae. It is divided broadly into two groups, viz. (a) Cryptogamae (non-flowering plants) and (b) Phanerogamae (flowering plants).

(a) Cryptogamae are divided into three groups, viz. (i) Thallophyta (they are undifferentiated into root, stem and leaf and include algae, fungi, lichens, and bacteria); (ii) Bryophyta (they are non-vascular plants and include liverworts, anthoceros or hornworts, and mosses); and (iii) Pteridophyta (they are vascular, non-flowering, non-seeded plants and include equisetum, lycopod, psilotum, and pteris); and
(b) Phanerogamae are divided into (iv) Gymnosperms (these are vascular, flowering, naked seeded plants and include conifer, cycas, ginkgo, and gnetum); and (v) Angiosperms (these are vascular, flowering, covered seeded plants and include monocot—seed with one cotyledon, dicot—seed with two cotyledons plants).

Pteridophytes and phanerogams together form tracheophyta (vascular plants), while phanerogams (gymnosperms and angiosperms) constitute the spermatophyta (seed plants).

6.2.3.1 Thallophyta

(a) **Algae**

Algae are green thallophytes that contain chlorophyll. In many Algae, other pigments like brown, red, blue-green are also present besides chlorophyll. The commercially important algae are limited to the diatoms and marine forms of brown and red algae. Alginic acid is prepared in large quantities from brown seaweeds (Phaeophyta). Species of *Macrocystis*, *Ascophyllum,* and *Laminaria* (e.g., *Macrocystis pyrifera*, *Ascophyllum nodosum*, *Laminaria hyperborea*) are commonly used for the preparation of alginic acid. Red algae (Rhodophyta) are characterized by red pigment—phycoerythrin and storage product Floridean starch—an amylopectin stains red with iodine. Agar or agar-agar, a heterogeneous polysaccharide (agarose and agaropectin), is the dried colloidal concentrate prepared from the decoction of various species of the genus Gelidium (*G. crinale* of Gelidaceae) and Gracilaria (*G. verrucosa*, *G. textorii* of Gracilariaceae). Different bioactive compounds with antioxidative, anti-inflammatory, and anticancer properties may be derived from algal sources including *Spirulina platensis*, *Ishige okamurae*, *Lobophora variegata*, *Sargassum vulgare*, *Spatoglossum schroederi*, *Fucus vesiculosus*, *F. serratus*, *Eisenia bicyclis*, *Ecklonia cava*, *E. kurome*, *Pelvetia canaliculata*, *Caulerpa cupressoides*, *C. Mexicana*, *Dunaliella tertiolecta*, *Capsosiphon fulvescens*, *Ulva fasciata*, *U. lactuca Polyopes affinis*, *Neorhodomela aculeate*, *Laurencia glandulifera*, *Porphyra yezoensis*, *Lithothamnion corallioides*, *Plocamium telfairiae*.

Agar and alginic acid, because of their abundant mucilage content, are used as demulcents and nutritives. Algae including macrophytic marine algae are important source of vitamins, minerals, proteins, fatty acids including polyunsaturated fatty acids, sulphated polysaccharides, halogenated furanones, brominated phenols, phloroglucinol (a phenolic compound), and oxygen heterocyclics, nitrogen heterocyclics, guanidine derivatives, phenazine derivatives, kahalalide F, lectins, fucoidans, kainoids, aplysiatoxins, polyphenols, phycobiliproteins, sterols that function as antioxidant, anticancer, antiviral therapeutic principles and fight against various diseases (e.g., cancer, chronic inflammation, atherosclerosis, diabetes, and cardiovascular disorder) and aging processes (Kohen and Nyska 2002; Pulz and Gross 2004; Plaz et al. 2008; Ajit et al. 2011; Lee et al. 2013; Yoon et al. 2017).

(b) **Fungi**

Fungi are classified into five major classes: Myxomycetes or slime fungi, Phycomycetes or alga-like fungi, Ascomycetes or sac fungi, Basidomycetes or club fungi, and Deuteromycetes or imperfect fungi. Ergot is a drug of fungal origin. Ergot of Rye (*Secale cereal* L.) is an important member of the class Ascomycetes. It is the dried sclerotium of a fungus, *Claviceps purpurea*, arising in the ovary of the rye plant. The main source of the crude drug is the controlled field cultivation of rye plant. Six pairs of alkaloids predominate in the sclerotium and are classified as water soluble (ergometrine or ergonovine) and water insoluble (ergotamine or ergotoxine). Yeast belongs to the genus Saccharomyces and *Saccharum cerevisae*, *S. carlsbergensis, and S. monacensis* are used in the industry. Yeast contains about 73% of moisture, 13% proteins (partly free and partly combined with nucleic acid), 0.27% of oil, certain % of vitamins (B complex, D_2, D_4, etc.), and enzymes (invertase, maltase, diastase zymase, etc.). Mushrooms exposed to sunlight or UV radiation are an excellent source of dietary vitamin D2 because they contain high concentrations of the vitamin D precursor, provitamin D2 and in addition, ingestion of mushrooms may also provide the consumer with a source of vitamin D3 and vitamin D4 (Keegan et al. 2013).

A wide range of medically active compounds that have been isolated from fungi include antibiotics, anticancer drugs, cholesterol inhibitors, psychotropic drugs, immunosuppressants, and even fungicides. Different antifungal, antiviral, and antiprotozoan principles have been isolated from fungi (Engler et al. 1998). Many edible species have been shown to produce medically significant metabolites. *Morchella esculenta* contains the amino acid, *cis*-3-amino-L-proline; *Ustilago maydis* synthesizes ustilagine and ustilagic acid; *Ganoderma lucidum* contains *p*-hydroxybenzoic acid, cinnamic acid, and lanostane-type triterpenoids such as ganoderic acids; *Hydnellum peckii* produces atromentin, an anticoagulant, *Schizophyllum commune* produces, an anticancer agent; *Saccharomyces* is used to produce the amino acid lysine, recombinant proteins insulin, Hepatitis B surface antigen, artemisinin, as well as insulin analogs. (Khanna et al. 1965; Mantovani et al. 1997; Zheng et al. 2006; Juárez-Montiel et al. 2011; Liu et al. 2012; Piotrowski et al. 2015).

6.2.3.2 Bryophyta

Bryophytes are classified into (i) Hepaticopsida (Liverworts), (ii) Anthocerotopsida (Hornworts), and (iii) Bryopsida (Mosses). They represent a diverse group of green land plants to develop during the process of evolution in antiquity, and more than 20,000 species are known worldwide. Although adapted to land habitat, Bryophytes are considered the amphibians of the plant world, because they require abundant moisture to complete their life cycle and growth. Various species of bryophytes have been used in different ways since antiquity due to medicinal quality, water

retention capacity, environmental contribution, and importance in ecosystem (Preet and Vashishtha 2015).

Bryophytes are popular remedy among the tribal people across the world and are used to cure hepatic disorders, skin diseases, cardiovascular diseases, used as antipyretic, antimicrobial, wound healing, and many more other ailments; and apart from ethno-medicinal uses some bryophytes possesses antitumor activities against different cancer cell lines (Singh et al. 2011; Chandra et al. 2017). Harris (2008) listed about 150 species of bryophytes along with their medicinal use and mentioned that bryophytes were mostly explored by Native North Americans (28%) and Chinese (27%) people for medicinal purposes. *Marchantia polymorpha* was used in the treatment of pulmonary tuberculosis, liver-related ailments and also boil as reported by Pant and Tewari (1989) from India. The treatment of liver diseases with liverworts represents an exceptional illustration of the 'Doctrine of Signatures'. Similarly, *Riccia* spp. was used to treat ringworm due to its morphological resemblance with the ring made by infections (Glime 2007). The liverworts posses definite biological activity and effect (Suire 1972; Wu 1977; Ando and Matsuo 1984) and the curative properties might be due the presence different bioactive compounds as members of bryophytes including liverworts contain diverse metabolites like lipophilic mono-, sesqui-, and diterpenoids, aromatic compounds (bibenzyls, bis-bibenzyls, benzoates, cinnamates, long-chain alkyl phenols, naphthalenes, phthalides, isocoumarins), several unsaturated lipids, fatty acid esters, flavonoids, phenolics, acetogenins (Tutschek and Rudolph 1971; Hart 1981; Asakawa 1982, 1984, 1990, 1995). In a screening work, Cambie et al. (1961), however, did not found alkaloids, leucoanthocyanins, saponins, triterpenes, and steroids from 251 mosses in a mammoth task from New Zealand.

Representatives of several moss genera, e.g., tea prepared from *Polytrichum commune* and water extract of *Sphagnum* (peat moss) is believed to have medicinal value. Due to absorbent capacity and antiseptic properties, *Sphagnum* has much more medical significance than other mosses and makes a better dressing than cotton. Gupta and Singh (1971) demonstrated the antibacterial activities of two mosses (e.g., *Barbula* and *Timella*) against 33 bacterial species. The traditional use of bryophytes for burns, cuts, wounds, and skin disease would suggest their probable protective action against the microbial pathogens (Ando 1983; Pant and Tewari 1990; Saxena and Harinder 2004). The plants *Chiloscyphus polyanthus*, *Diplophyllum albicans*, *Polytrichum juniperinu*, etc., may be used for curing deadly cancer while *Marchantia ploymorpha*, *M. stellata*, *Diplophyllum taxifolium*, *Diplophyllum albicans*, *Polytrichum commune*, *Wiesnerella denudata* for the tumor suppression. This plant group is of great importance because of its chemical variability and diversity. At present, only a minor fraction ($\sim$5%) of the total bryophytes has been studied chemically.

6.2.3.3 Pteridophyta

Pteridophytes, according to the summarized classification proposed by Smith (1955), Bold (1957), and Zimmerman (1959), are grouped into four divisions, viz. (i) Psilophyta (e.g., Rhinia and Hornea—fossil genera, Psilotum, and Tmesipteris—living genera); (ii) Lycophyta (Club mosses, e.g., Selagenella, Lycopodium, Isoetes); (iii) Sphenophyta (Horsetail, e.g., all fossil except Equisetum); and (iv) Pterophyta (Ferns or Filicophyta, e.g., Marselia, Salvinea, Azolla, Adiantum, Pteris). Pteridophytes are represented by about 305 plant genera and more than 13,000 species all over the world, and by virtue of their great diversity, esthetic property and medicinal value, pteridophytes have been known to naturalists, plant lovers, and herbalists for centuries.

Pteridophytes contain a variety of secondary metabolites such as alkaloids, glycosides, flavonoids, terpenoids, sterols, phenols sesquiterpenes. (Singh 1999; Kulandairaj and John 2000). The reported antimicrobial potential of pteridophytes (Benerjee and Sen 1998; Kumar and Kaushik 1999; Parihar and Bohra 2002, 2003) may be due these metabolites as well as the medicinal activities of pteridophytes against different ailments rely on these metabolites. Although pteridophytes are relatively poor in nitrogen-containing secondary metabolites, the lysine-derived alkaloids (e.g., lycopodine, huperzine A, from Lycopodiaceae) and ornithine-derived palustrines (from Equisetaceae) are known (Ayer 1991; Cramer et al. 2015). The entire pteridophytic plant or parts (e.g., fronds, and/or rhizome) are used as drug source of astringent, antihelmintic, styptic, diuretic, cough, fever, scabies, asthma, women's sterility, hectic fever, dyspepsia, Alzheimer's disease, cancer rheumatism, diabetes, inflammation, bronchitis, hepatoprotective, sedative chronic disorders, mollusks, hallucination, leprosy, fertility, antioxidant, antimicrobial, ulcers, pesticides, and others (Perumal 2010; Singh and Singh 2015).

The leaf and root decoction of *Adiantum lunulatum* has been found to be very effective in the treatment of chest complaints (Nair 1959; Rout et al. 2009). The fresh fronds of *Blechnum orientale* are used as a poultice for boils; the rhizome is used as an anthelmintic, as cure for intestinal worms, bladder complaints, etc. (Dixit and Vohra 1984). The rhizome and roots of *Cheilanthes tenuifolia* are used by the tribals as general tonic (Dixit 1959). Rhizome of *Dicranopteris linearis* is used as anthelmintic, and fronds are used for asthma (Manickam and Irudayaraj 1992). The rhizome of *Drynaria quercifolia* is bitter and is used as antibacterial, anti-inflammatory, for treating constipation, diarrhea, ulcers, and other inflammations. The decoction of plant is used in typhoid fever, and fronds are useful in treating swellings (Dixit and Vohra 1984; Warrier et al. 1996). The rhizome of *Lygodium flexuosum* is boiled with mustard oil and locally applied in rheumatism, sprains, scabies, ulcers, eczema, and cuts (Dixit 1959; Dixit and Vohra 1984).

6.2.3.4 Gymnospermophyta

Gymnosperms may be shrubs, woody trees, or rarely vines, viz. Ephedra, Pinnus, Abies, Ginkgo, Gnetum, etc., Gymnosperm consists of 4 classes (Cycadopsida, Ginkgopsida, Gnetopsida, and Pinopsida) and about 861 species of plants. *Pinus roxburgii*, *P. wallichiana*, *Cedrus deodara*, *Abies pindrow,* and *Taxus wallichiana* are prominent gymnosperms. Gymnosperms form an important group of plants by way of their immense ecological and socioeconomic value providing timber, fuel, resins and gums, medicinal and other useful products. *Taxus wallichiana*, *Ephidra,* and *Juniperus* species provide many drug principles.

Secondary metabolites possess a number of biological properties such as anti-apoptosis, antiaging, anticarcinogen, anti-inflammation, antiatherosclerosis, cardiovascular protection and improvement of endothelial function, as well as inhibition of angiogenesis and cell proliferation activities. Gurav et al. (2013) in a phytochemical screening work reported the presence of several secondary metabolites like saponins, phenols, tannins, flavonoids, triterpenes, and phytosterols in some ornamental gymnosperms viz, *Araucaria hetrophylla*, *Cycas circinalis*, *Thuja occidentalis,* and *Zamia furfuracea* while Pusthija et al. (2014) analyzed various phenolic compounds some gymnosperm species and along with their bioactive properties, especially as a allelochemicals. Gymnosperms are relatively poor in nitrogen-containing secondary metabolites. However, some are present in few cases such as the methyl azoxymethanol glycosides and α-amino-β-methylaminopropyonic acid (Cycadales), aminohydroxycinamates of taxanes (Taxaceae), the tyrosine derived homoerythrines and cephalotaxins (Cephalotaxaceae), the benzyltetrahydroisoquinolines (Gnetaceae), taxiphyllin, ephedrine and ephedroxane (Ephidraceae), and acetate-derived pinidine (Pinaceae). Ethnobotanical data on gymnosperms provide valuable information about the medicinal use of the gymnosperms. Chopra (1992) described and highlighted the importance of gymnosperms in nature and in human life. They are commonly used as expectorants for coughs and lung congestion, diaphoretics for fevers, antirheumatics for arthritis, and antiseptics and astringents for topical use.

Cycas seeds are used as an emetic and a cure for boils, and sores. *C. rumphii* pollen is believed to be narcotic. The powdered stem of *C. pectinato* is used as hair wash for diseased hair roots. Zamia seeds yield a poisonous substance that acts as a cure for gout and pains. The peculiar odor of Cycas male cones drives away bugs and sometimes even rats from fields or stored grains. Essential oils extracted from conifers are used to some extent in perfumery, or in the preparation of insect repellents, deodorants, and certain medicines for skin ailments. Seeds of *Ginkgo biloba* are used in the cosmetics industry in China and Japan. Unripe seeds are collected and the pulp of the seed coat is utilized. The leaf extract of *G. biloba* is useful in the treatment of cerebral insufficiency and vertigo. Ginkgolide compounds also mollusks platelet activating factor (PAF) in vertebrate systems.

Ephedra is a medicinally important gymnosperm. The alkaloid ephedrine is extracted from the green branches of different Ephedra spp. (e.g., *E. gerardiana*, *E. equisctina*, *E. sinica*). Ephidrine is an important ingredient of cough mixtures

and nasal drops; it dilates the bronchial tube and contracts the mucous membrane. Ephedrine exerts a sympathomimetic action similar to that of adrenaline. *E. gerardiana* is used in treatment of bronchitis, asthma, and relieving bronchial spasm, cardiac and circulatory stimulant as well as in hepatic diseases, as blood purifier and cleaning of teeth; and decoction of stem and roots is used as remedy for rheumatism and syphilis. 'Ma huang' (*Ephedra sinica*) has been in use in China for more than 5000 years for the treatment of asthma. The seeds are used as cooling medicine.

Essential oils, balsams, and insecticides Colophony of Pinaceae are of pharmaceutical and industrial interest. Monoterpenoids (alpha pinene and borneol) are the main constituents of essential oils and balsams. Flavonoids, condensed tannins, and lignans are widely present in the members of this family. *Cedrus deodara*, *Pinus roxburgii*, *P. wallichiana*, and *Abies pindrow* are prominent gymnosperms of are source of timber, fuel wood, and pharmaceutical principles.

The wood of *Cedrus deodara* is carminative, diaphoretic, useful in fever flatulence, pulmonary and urinary disorders, rheumatism, piles, stone in kidney, and also antidote to snake bite. Bark is astringent, useful in fever, diarrhea, and dysentery. Oil is diaphoretic, useful in skin diseases and for ulcer. Oil extracted from root is used for skin diseases of goats and camels. Oleoresin and dark-colored oil or turpentine, are applied to ulcers and skin diseases. They are valuable in horses and sore feet of cattle. In India, *Cedrus deodora* oil is used in perfumery and soaps. Resin of *Pinus roxburgii* is stimulant. Internally it is used as stomachic and as remedy for gonorrhea. Externally it is applied as a plaster to buboes and abscesses for suppuration. Wood is diaphoretic and stimulant, used in burning of body, cough, fainting, and ulceration. Wood and oleoresin is used in snake bite and scorpion sting. The oil has irritant action, and most of its medicinal uses are due to that property. In controlled small doses, it acts as a stimulant expectorant and is useful in chronic bronchitis. It cures flatulent. It has limited use also in typhoid, minor hemorrhages (such as from gums, nose). Given as an enema, it cures constipation. Its commonest use, however, is as liniment in rheumatic pains. Inhaling the vapors of turpentine is useful in bronchitis. Wood is aromatic, antiseptic, deodorant, and stimulant, diaphoretic, refrigerant, rubefacient and carminative. Oleoresin is used for fumigations. Essential oil is used with success as a stimulant diuretic in gleet, long-standing gonorrhea. The tar is employed for chronic bronchitis phthisis and in skin diseases. Resin is also used as hair remover. *Pinus wallichiana* is used similarly as *Pinus roxburghii*.

Tincture or decoction of the dried terebinthinous leaves of *Abies pindrow* is useful in case of cough, phthisis, asthma, chronic bronchitis, and catarrh of the bladder and other pulmonary affections. Juice of the fresh leaves is administered in fever of infants during dentition and also in affections of the chest. Powder of leaves is given with juice of *Adhatoda vasica* and honey in cough, asthma, and haemoptysis.

Some species of *Podocarpus* are used in systems of traditional medicine for conditions such as fevers, coughs, arthritis, sexually transmitted diseases, and canine distemper *(*Abdillahi et al. 2011). A chemotherapy drug used in treatment of leukemia is made from *Podocarpus* (Ogren 2015). The fruit and wood of

Cupressussem pervirens are anthelmintic and astringent. Pollen grain causes hay fever. Infusion of berries of *Juniperus communis* is diuretic. Berries, wood, and oil reported to be used in folk remedies for cancer, indurations, polyps, swellings, tumors, and warts. Reported to be carminative, stimulant in dysmenorrhea, skin diseases, kidney diseases, deobstruent, diaphoretic, digestive, stimulant in dysmenorrhea, skin diseases, and kidney diseases and also used in alcoholic and non-alcoholic beverages. The fruit and oil are diuretic, carminative, stimulant, and is used in dropsy, gonorrhea, gleets, leukorrhea, and some cutaneous diseases. The berries are given in scanty urine, cough, and pectoral affections. Locally, powder of berries is rubbed on rheumatic and painful swellings. Ash of the bark is applied in certain skin affections. The berries are also recommended in infantile tuberculosis and diabetes. Juniper is used in stomach cramps, asthma. Twigs are burnt as incense and berries used similarly as that of *J. communis*. Fruits are diuretic, carminative, stimulant, and are used in dropsy, mollusks, gleets, leukorrhea and in some cutaneous diseases. Properties of the fruit are the same as of *Juniperus communis* and also used for flavoring the 'Gin' and other products. *J. squamata* twigs are burnt as incense and berries used similarly as that of *J. communis* and *J. sibirica.* The fruit and wood of *Thuja orientalis* are anthelmintic and astringent. Pollen grain may cause hay fever.

Many of the gymnosperm species can be used for treating arthritis, rheumatism and stomach disorders, fever, diarrhea, diabetes, jaundice, backache, stomachache, ulcers, cold, and even cancer. Lal et al. (1994) described fifty plant species (including *Taxus baccata*) that are used as ethnomedicines. Taxus (yew) is used for curing a number of ailments. Bark and leaves of *Taxus wallichiana* (Himalayan yew) yield a potential anticancer drug taxol. Tea of leaves is useful in high fever and asthma. Leaves are used in bronchitis, hiccough and asthma, for indigestion, epilepsy and as aphrodisiac. Leaves and fruit are sedative, antiseptic, and emmenagogue. Plant poisonous is used as fish poison. Leaves of *Taxus baccata* (European yew) are used in asthma, bronchitis, epilepsy, and indigestion. The plant contains a toxic principle taxine which is an active heart poison. Taxol, obtained from *T. brevifolia* (Pacific yew), has been effectively used as an anticancer drug (especially against ovarian, breast, and colon cancer). As a large number of yew trees are being felled to obtain this drug, efforts are now on to produce the chemical taxol through tissue culture.

6.2.3.5 Magnoliophyta

Magnoliophyta (Angiospermae) is divided into two classes, (i) Magnoliopsida (dicotyledons) and (ii) Liliopsida (Monocotyledons). Magnoliophyta (Angiospermae) includes 83 orders, 383 families, and ~250,000 species. These two classes are unequal in size, the Magnoliopsida contains ~64 orders, 318 families, 9600 genera, and 170,000 species and the Liliopsida with 19 orders, 65 families, and ~50,000 species. According to the IUCN, however, there are 59,300 species of monocots and in agriculture, the majority of the biomass produced comes

from monocots (http://cmsdata.iucn.org/downloads). These include true grasses of the family Poaceae such as major grains, forage grasses, sugar cane, bamboos, and also others like palms, bananas, gingers and their relatives, onions, lilies, daffodils, irises, amaryllis, cannas, bluebells, tube roses, tulips.

6.2.3.6 Characteristics of Monocot and Dicot Group of Plants

Monocot and dicot plants differ in growth form, leaf, root, stem, flower, pollen, and embryo characteristics as shown in Table 6.2.

Most of the medicinal and aromatic plants of belong to the families like Apiaceae, Apocynaceae, Ateraceae, Brassicaceae, Boraginaceae, Cesalpinaceae, Convolvulaceae, Caryophyllaceae, Cucurbitaceae, Euphorbiacea, Fabaceae, Lamiaceae, Malvaceae, Mimosaceae, Oleaceae, Papaveraceae, Phytolaccaceae, Ranunculaceae, Roseaceae, Rubiaceae, Rutaceae, Solanaceae, Scrophulariceae, Verbenaceae of Magnoliopsida and Liliaceae, Poaceae, Orchidaceae, Zingiberaceae

Table 6.2 Comparison of monocot and dicot plant characteristics

Feature	In monocots	In dicots
Growth form	Herbaceous and occasionally arboraceous	Arboraceous but in some cases herbaceous
Leaves	Simple, mostly isobilateral leaf, shape oblong or linear, often sheathed at base, petiole rare, stipules absent, usually parallel leaf veins	Simple or compound, mostly dorsiventral, broad, leaf sheath rare, petioles and stipules common, pinnately or palmately reticulate venation
Roots: vascular bundles	Fibrous root system is common, primary root of short lived, replaced by adventitial fibrous or fleshy root systems, radial vascular bundles, many in number	Taproot system is common, it develops from the radicle, secondary roots also develop, radial vascular bundles, few in number
Plant stem: vascular bundles	Vascular bundles many in number, scattered in undifferentiated ground parenchyma tissue, cambium and secondary growth absent, rarely present for anomalous secondary growth	Vascular bundles are few in number, arranged in ring form, ground tissue differentiated into cortex and stele, cambium and secondary growth present
Flowers: floral parts in multiples of 3, 4 or 5	Trimerous flower (parts in 3) or multiples of 3	Tetramerous (parts in 4) or pentamerous (parts in 5)
Pollen: number of apertures (furrows or pores)	Monocolpate (1 aperture or colpus)	Tricolpate (3 aperture or colpus)
Embryo: number of cotyledons (leaves in the seed)	Cotyledon 1, endosperm frequently present in seed	Cotyledon 2, endosperm present or absent

of Liliopsida. Distribution of medicinal plants by families (genus/family) may be approximately as Asteraceae-419, Euphorbiaceae-214, Lamiaceae-214, Fabaceae-214, Rubiaceae-208, Poaceae-168, Acanthaceae-141, Rosaceae-129, Apiaceae-118, etc., but it may vary depending on location, area, and many other environmental and anthropogenic factors. Patel (2012) recorded the distribution of medicinal plants among three families of an area as Asteraceae (28%), Fabaceae (47%), and Solanaceae (25%).

Apiaceae family members are generally herbs. The family is rich in essential oils; some species accumulate alkaloids and furanocoumarins, coumarins, terpenes, sesquiterpenes, and triterpenoid saponins. Essential oils from seeds and fruits of some of the plants are used for stomach disorders, flatulence, and against kidney stones. Important medicinal plants of the family are *Carum carvi* (carminative and spice), *Coriandrum sativum* (carminative and spice), *Cuminum cyminum* (carminative and spice), *Ammi majus* (for skin ailments), *Anethum graveolens* (carminative and spice), *Foeniculum vulgare* (mild carminative and eye wash), *Pimpinella anisum* (expectorant, spasmolytic and carminative), and *Trachyspermum ammi* (carminative, source of thymol). *Apium graveolens* (to treat diabetes, stomach, and skin problems), *Daucus carota* (diuretic, stimulant, deobstruent), *Eryngium maritimum* (to treat coughs, bronchitis, asthma, consumption, liver affections, kidney diseases), *Petroselinium crispum* (to treat digestive disorders, high blood pressure, menstrual disorders), *Conium maculatum* (as a medicine, it is sedative and antispasmodic, and in sufficient doses acts as a deadly poison), *Smyrnium olusatrum* (bitter and digestive).

Members of Apocynaceae are a rich source of indoline alkaloids, steroidal alkaloids, and cardioactive glycosides. Cyanogenetic glycosides, saponins, tannins, coumarins, phenolic acids, triterpenoids, etc., are some other chemical constituents of Apocynaceae. Important medicinal plants of the family are: *Alstonia scholarasis* (cardioactive), *Catharanthus roseus* (leukemia anticancer), *Holarrhena antidysenterica* (bitter and antidysenteric), *Nerium indicum* (cardioactive), *Rauwolfia serpentina* (hypotensive), *Strophanthus kombe* (diuretic), *Thevetia nerifolia* (cardioactive), etc.

Asteraceae family members bear a complex inflorescence (the capitula). Storage of carbohydrate in the form of inulin is a characteristic feature of this family. Other chemicals include sesquiterpene lactones, polyacetylenic compounds and essential oils, alkaloids (pyridine, quinoline, diterpenoid, and pyrrolizidine group) in small amounts, diterpene glycosides, etc. Some members of this family show antitumor or antibacterial activity. Important medicinal plants of the family are *Chrysanthemum cinerarifolium* (insecticide), *Artemisia cina* (anthelmintic), *Artemisia annua* (antimalarial), *Artemisia absinthium* (bitter tonic and choleretic), *A. absinthum*, *Calendula officinalis* (topical use for skin infections), *Arnica montena* (externally in hair preparations and for bruises), *Echinacea angustifolia* (immunostimulant), *Gynura procumbens* (antidiabetic, hypotensive), *Stevia rebaudiana* (stevioside; sweetener for soft drinks), *Chicory intybus* (hepatoprotective), *Matricaria chamomillia* (tonic, stimulant and cosmetics), and *Silybum marianum* (skin ailments, hepatoprotective). *Matricaria chamomilla*, *Anthemis nobilis*, *Bellis annua*,

Senecio bicolour, *Cichorium intybus*, *C. spinosa*, *Cynara cardunculus*, *C. cardunculus*, *Senecio bicolour*, *Silybum marianum* are some other medicinal plants of the family.

Members of Boraginaceae are herbs or small shrubs with bristly stems and leaves. Examples in this family include *Borago officinalis* (in the treatment of coughs, flu and bronchitis), *Heliotropium indicum* (eye disease), *Symphytum officinale* (astringent), *Anchusa asurea* (diuretic), *Neatostema apulum* (cough, diuretic), *Echium vulgare* (used in traditional medicine), and *Cynoglosum creticum* (rheumatic pain).

Brassicaceae includes annual herbs. Many members contain mustard-oil glycosides, and some genera contain cardiac glycosides. Seeds of some members of this family are rich source of fixed oils, condiments, rubefacient, counter-irritant, etc. *Brassica campestris* (mustard), *B. alba* (white mustard), *B. nigra* (black mustard), and *B. napus* (rape seed) are different important members of the family. Other members of the family minor medicinal value are *Cheiranthus cheiri*, *Cardamine 24ollusk*, *Capsella bursa-pastoris*, *Armoracia rusticana*, *Sisymbrium officinale*, *Raphanus raphanistrum*, *Nasturtiumofficinale*, etc.

Caryophyllaceae family group plants usually have four- to five-petaled flowers that are usually white or pink in color. Several members of Caryophyllaceae are widely used in traditional medicine, especially in CTM as anticancer, antibacterial, antifungal, antiviral, antioxidant, and anti-inflammatory agents. They also possess other properties such as ribosome inactivation, inhibition of prostatic enlargement in rats, inhibition of intestinal enzyme carboxyelasterase in rats, cerebro-protective activity, and antiobesity in rats. Major chemical constituents of Caryophyllaceae are saponins, phytoecdysteroids, benzenoids, phenyl propanoids, and nitrogen-containing compounds; and the most important property of plants of the family is anticancer activity and is shown by the large number of plant species studied. Examples from this family include *Arenaria serpyllifolia*, *Stellaria media*, *Spergularia rubra*, *Paronychia argentea*, *Herniaria glabra*, and *Alsina tenuifolia*.

Convolvulaceae family members are herbaceous and more rarely subwoody-to-woody, perennial climbing plants with underground parts sometimes swollen into tuberous roots. Chemical constituents of the family include indole, isoquinoline, pyrrolidine and tropane and pyrrolizidine alkaloids. Purgative resins, phenolic acids, and triterpenoid saponins are also reported in some species. Important medicinal plants of the family are *Ipomoea hederacea* (purgative), *Cuscata reflexa* (hypotensive), *Ipomoea sepiaria* (strong purgative), *Argyreia speciosa* (roots in rheumatic afflications and leaves in skin diseases and wounds).

Cucurbitaceae family contains a large number of crop and wild species that are medicinally valuable. Cucurbitacins of cucurbits constitute an important group of secondary metabolite compounds consisting of diverse highly oxygenated tetracyclic triterpenoid substances which are known for their bitterness and toxicity. In addition to these, they are rich in carbohydrates, protein, vitamins, amino acids, and minerals. Cucurbitacins are arbitrarily divided into twelve categories such as cucurbitacins A–T. These have prominent anticancer (human colon, breast, lung cancer) properties. Seed, fruit, or other parts of some cucurbits possess purgatives,

emetics, and antihelmintics properties due to cucurbitacin content. A few cucurbitacins are also known for their cytotoxic, hepatoprotective, anti-inflammatory, and cardiovascular effects. Charantin (mixture of sterol glucosides), vicine (pyrimidine nucleoside), insulin like polypeptides, 25ollusks glycosides (isovitexin, saponarin, acylated mollusks C-glycosides), phenolic glycosides, echinatin, saponins, amarinin, luffein, β-sitosterol, echinatol A and B, oleanolic acid, multiflorane triterpenoids, abortifacient proteins (momorcharin, luffaculin, trichosanthin, β-trichosanthin), etc., are also present in some species. Cucurbits are used as a remedy for different ailments like night blindness, dropsy, anthelmintic, gonorrhea diseases, peptic ulcer, haemoptysis, respiratory trouble, hemorrhoids, leprosy, splenitis, and heart disease. Some of the medicinally important cucurbits are *Benincasa hispida* (used for the management of peptic ulcer, hemorrhages from internal organs, asthma, cough, diabetes, epilepsy, and other nervous disorders), *Citrullus colocynthis* (fruits are bitter, acrid, cooling, cathartic, carminative, antipyretic, anthelmintic, free radical scavenging and antioxidant, useful in hypoglycemia, tumors, ascites, leucoderma, ulcers, asthma, bronchitis and constipation), *Coccinea cordifolia* (hypoglycemic), *Cucurbita pepo* (antioxidant, fruit is cooling and astringent to the bowels, increases appetite, cures leprosy and purifies the blood, seeds cure sore chests, haemoptysis, bronchitis, and fever), *C. andreana* (anticancer and cyclooxygenase-2 (COX-2) inhibitory), *C. ficifolia* (use in the treatment of wounds, hemorrhoids, fever, diabetes type 2), *C. maxima* (antitumor, antiobesity, hepatoprotective, diuretic, antioxidant), *Cucumis sativus* (fruit is demulcent, seeds are cooling, tonic, diuretic, and anthelmintic), *Cucumis melo* (fruit is tonic, laxative, galactagogue, diuretic, diaphoretic shows high Superoxide Dismutase—SOD activity, used in eczema treatment), *Ecballium elaterium* (fruit juice was used in the treatment of constipation, jaundice, otitis, and headache), *Lagenaria siceraria* (antihyperlipidemic, cardioprotective, cures pain, ulcers, fever, pectoral cough, asthma, and other bronchial disorders), bitter luffa (cure conjunctivitis of the eye, jaundice), *Luffa echinata* (hepatoprotective), *L acutangula* (helpful in blood purification, skin treatment, ringworm, piles, removal of kidney stone, and leprosy), *Momordica charantia* (antihyperglycemic, anthelmintic, antiemetic, carminative, purgative, antioxidant), *M. cochinchinensis* (fruits for the treatment of ulcer, piles, sores, and obstruction of liver and spleen, seeds for chest problems and diuretic, roots for removing piles, migraine, excess sweating, cough, and stones), *Sechium edule* (antihypertensive), *Trichosanthes kirilowii* (cough medicine, expectorant), *T. cucumerina* (cathartic, anti-inflammatory, antidiabetic, antifebrile, anthelmintic, gastroprotective), *T. dioica* (febrifuge, lower cholesterol activity, and blood sugar), *T. tricuspidata* (laxative, anthelmintic), *Wilbrandia ebracteata* (roots and tubers produce anti-inflammatory, analgesic antitumor effects, and inhibition of arthritis), etc.

Euphorbiaceae family members are mostly herbs, but some are shrubs or trees, and some others are succulent and resemble cacti. Milky latex is a characteristic of the members of Euphorbioideae (poisonous latex) and Crotonoideae (innocuous latex). White mangrove (*Excoecaria agallocha*) latex causes blistering on contact and temporary blindness if it contacts the eyes. The family contains a large variety

of phytotoxins such as diterpene esters, alkaloids, glycosides, and ricin-type toxins. Important medicinal plants of the family are *Ricinus communis* (laxative), *Croton tiglium* (laxative), *Euphorbia peplus* (for skin cancer and actinic keratosis), *Euphorbia tirucalli*, (pugative, anantibacterial, molluscicide, antiherpetic, and antimutagenic). *Euphorbia hirta*, *Manihot esculenta*, *Jatropha curcas*, *Hevea brasiliensis*, *Euphorbia pulcherrima*, etc., are some other plants of interest.

Lamiaceae or Mint family members are mostly herbs with square stem and verticillaster inflorescence. Stems and leaves are characterized by the presence of glandular hairs containing aromatic volatile oil. Volatile oils, menthol and thymol, diterpenoids and triterpenoids, saponins, polyphenols, tannins, iridoids, and their glycosides and coumarins are the major chemical constituents of this family. Pyridine and pyrrolidine alkaloids are also present. Important medicinal plants of the family are *Ocmium sanctum* (antipyretic, respiratory problems); *Ocimum basilicum* (cold diseases, prophyloxis, tooth diseases, perfumes, cosmetics); *Mentha arvensis* (for respiratory problems); *Mentha piperita* (source of menthol, flavoring, carminative) and other *Mentha* spp., *Marrubium vulgare* (in lung troubles and coughs), *Melissa officinalis* (carminative, diaphoretic and febrifuge), *Micromeria microphylla* (antiseptic), *Thymus vulgaris* (antispasmodic) and other *Thymus* spp., *Rosemarinus officinalis* (carminative and spasmolytic); *Salvia officinalis* (topical antiseptic and orally as a carminative and spasmolytic); *Lavendula angustifolia* (carminative and spasmolytic) and the *Lavendula* spp.; *Leucas aspera* (antipyretic) contains glucosides, tannins, saponins in leaf; *Leucas lavandulaefolia* (vermifuge) contains alkaloids, flavonoids, tannins, steroids, saponins, glycosides, etc.; and *Leucas zeylanica* (used against headache, fever, scabies, etc.) and *Origanum vulare* (antiflatulent, antirheumatic, and healing of wounds).

Leguminosae or bean family is divided into three sub families: Papilionaceae, Mimosoideae, and Caesalpinoideae; includes herbs, shrub, trees, twiners, or climbers. Fruit is a legume or a pod. (i) Papilionaceae or Fabaceae contains chemical constituents like flavonoids and tannins as common. Quinolizidine and pyrrolizidine alkaloids are specific to certain genera; Isoflavonoids, coumarins, and saponins are other important phytoconstituents repoted in many species. Lectins, high molecular weight sugar-binding proteins are present in the seeds of many species. Phasin from *Phaseolus* species is toxic to mammals. Important medicinal plants are *Psoralea corylifolia* (various skin infections), *Glycine hispida* (source of proteins), Mucuna pruriens (parkinsonism), *Arachis hypogea* (fixed oil), *Astragalus gummifer* (demulscent, suspending, and emulsifying agent), *Cyamopsis tetragonolooba* (antidiabetic, source of guar gum); *Myroxylon balsamum* (Tolu balsam in cough syrup, antiseptic), *Myroxylon balsamum* var. *pereirae* (Peru balsam used in hemorrhoid suppositories and ointment, cough medicine) *Trigonella foengraceum* (antiseptic and expectorant, source of steroids), *Astragalus tragacanthus* and also *A. adscendens*, *A. gummifer*, *A. brachycalyx* (demulscent, suspending, and emulsifying agent); *Indigofera tinctoria* contains apigenin, indigotin, kaempferol, rotenol, rotenone, tephrosin, and sumatrol in various plant parts and used for the treatment of fever, liver and spleen disorders, rheumatoid arthritis, gout, gray hairs, etc.;

Glycyrrhiza glabra (expectorant) contains anethole, glycyrrhizin, and phytoestrogens like isoflavene glabrene and isoflavane glabridin.

(ii) Caesalpiniaceae contains chemical constituents like anthraquinones as major and diterpene alkaloids are also reported in some taxa. Important medicinal plants are *Cassia acutifolia* (laxative), *Cassia angustifolia* (laxative), *Caesalpinia sappan* (sappanwood and Indian redwood), *Cassia tora* (laxative), *Cassia occidentalis* (laxative), *Cassia fistula* (laxative), and *Tamarindus indica* (laxative).

(iii) Mimoseae includes tannins and polysaccharides as common constituents. Important medicinal plants are *Acacia arabica* (gums), *Acacia catechu* (astringent), *Acacia farnesiana* (perfumery), and *Albizzia lebbek* (antipoisoning).

Malvaceae family includes plants having five-petaled flowers and a nutlet-like fruit. It contains several vitamins an essential oil, tannins and flavonoids (hypolaetin and gossypin), phenolic compounds, phenylpropanoids, etc. Examples include *Malva sylvestris* (expectorant), *Gossypium herbaceum* (abortifacient, seed oil gossypol has male contraceptive, antifungal, and antibacterial properties), *Alcea rosea* (expectorant and anti-inflammatory), *Althaea rosea*, *Althaea officinalis* (antifungal and antibacterial, antiviral and antitumor properties), and *Hibiscus sabdariffa* (hypotensive, flavors, drinks).

Oleaceae contains of shrubs and trees, and a few members of the family are lianas. A number of phytochemicals such as glycosides, secoiridoid, flavonoids, and polyunsaturated fatty acids are present in different members of the family. The flowers are highly odoriferous and the notable members are *Olea europaea* (diuretic, hypotensive, emollient, laxative, febrifuge, skin cleanser); *Fraxinus* spp. (cure warts and rickets); Jasminum officinale (antidepressant, aphrodisiac); *Jasminum grandflorum* (cosmetics, perfumes, flavors); *Ligustrum* spp., Chinese *Ligustrum* sp. Is used in traditional herbal medicine; Forsythia spp., *Forsythia suspensa* is considered one of the 50 fundamental herbs in Chinese herbology; Chionanthus virginicus (white fringetree); and Syringa vulgaris (common lilac). The olive oil from *O. europaea* is produced by pressing whole olive.

Papaveraceae family members contain a latex or watery sap. There are four petals in a flower and these are cross-shaped with two opposite petals above the other two. The isoquinolinic alkaloids are present in the family. Members of Papaveraceae contain alkaloids such as chelidonine, morphine, codeine, papaverine, narcotine, thebaine, oripavine, protopine, isoboldine, and fumarine; saponins, Flavonols, kaempferol, quercetin, cyanogenic glycoside compounds (dhurrin and triglochinin), meconic acid and chelidonic acid, as well as; and a trace of essential oil and pigments. Plants with a medicinal value include *Argemone mexicana* (antimicrobial, antidiabetic, antioxidant, and hepatoprotective), *Chelidonium majus* (used in parasitic skin problems, strong laxative, in the treatment of jaundice, kidney problems, and cancer), *Papaver somniferum* (sedative, nerve relaxant), *Papaver rhoeas* (used for the treatment of insomnia, coughs, and mental disturbances), *Glaucium flavum* (sedative), *Fumaria officinalis,* and *F. capria capreolata* (blood purifier, smooth muscle relaxant, sedative, and antibacterial).

Ranunculaceae family members are characterized by showy flowers that usually have 5 petals. There are a wide range of drugs and poisons found in the

Ranculaceae. Many compounds serve both purposes; some can cure diseases at one dosage and kill at a higher one. These compounds are alkaloids, damascenine alkaloid, delphinine alkaloids, cadiac glycosides, saponins, tannins, vitamin C, acetyloleanolic acid, and many toxic compounds. Examples from this family include *Adonis annuus* (poisonous, used as a diuretic, tonic, in the treatment of heart failure), *Ranunculus ficaria* (used in the treatment of hemorrhoids), *Anemone coronaria* (anti-irritant and pain reliever), *Nigella damascene* (used to mask the unpleasant taste of medicines, in the treatment of high temperatures, regulate menstruation, and against tapeworm), *Nigella ollus* (chest diseases, diuretic), *Delphinium ajacis* and *D. staphysagria* (used in the treatment of head-lice infestations), *Clematis vitalba*, *Clematis cirrhosa* (pain reliever).

Rosaceae family members are mostly trees or shrubs with variable characteristics. A large number of species in Rosaceae possess medicinal value, and large number of chemicals have been identified including sugars, organic acids, terpenoids, essential oils (rose oil) and flavonoids, cyanogenic glycosides, phloretin, tannins, vitamin A, B complex, C, E, K, and minerals, particularly potassium and iron in various plant parts (e.g., flowers, petals, rosehips, root, root bark). These chemicals are responsible for different medicinal properties such as astringent, antiseptic, diuretic, antihemorrhoidal, anti-inflammatory, headache remedy antidepressant, antiphlogistic, antispasmodic, antiviral, aphrodisiac, and tonic properties as well as insecticidal and vermicidal properties of different members of the family. Medicinal plants like *Crataegus monogyna* (hypotensive), *Cydonia oblongata*, *Fragaria moschata* (gum disease and a diuretic), *Rosa damoscena* and *R. centifolia* (rose oil), *R. gallica* (astringent), *Pyrusamyd aliformis*, *Eriobotrya japonica*, *Prunus persica*, *P. spinosa* and *Pyrus amydaliformis* (diuretic, sedative, laxative and antibacterial properties), *Rubus ulmifolius* (diabetes and ulcer), *Eriobotrya japonica* (astringent properties), etc., are some of the examples of this family.

Rubiaceae family members are herbs, shrubs, or trees with fibrous roots, sometimes annually enlarged (Ipecac). Chemical constituents of the family show a large diversity (e.g., indole, oxindole, quinoline, and purine-type alkaloids; catechins; anthraquinones, di and triterpenoids; irridoid glycosides). Important medicinal plants of the family are *Cinchona ledregiana*, *C. calisaya*, *C. officinalis*, *C. succirubra* (antimalarial, bitter tonic, and febrifuge), *Cephaelis ipecacuanha* (expectorant and emetic), *Uncaria gambier* (astringent), *Coffea arabica* (stimulant), *Morinda citrifolia* (abdominal pain, impotence, and menstrual disorders in TCM).

Rutaceae includes shrubs and trees. Essential oil is the common constituent of this family found in lysigenous secretory cavities in the parenchyma and pericarp. Membrane crystals and hespiridin are common. Furano and pyranocoumarins are the typical constituents of this family. Imidazole, acridone, and benzyltetrahydroisoquinoline type of alkaloids have been reported. Many of the fruits are rich source of Vitamin C and citric acid. Important Medicinal plants of the family are *Citrus aurantium* (flavoring agent), *Citrus limonia* (vitamin C), *Aegle marmelos* (immunomodulatory activity), *Ruta graveolens* (used as emmenagogue and spasmolytic), *Pilocarpus jaborandi* (pilocarpine, used in ophthalmology),

Murraya koenigii (improves heart function, fights infections), *M. paniculata* (antidiarrheal, antinociceptive, and anti-inflammatory).

Scrophulariaceae family includes herbs or undershrubs. Chemical constituents of the family are cardiac glycosides, bitter irridoid glycosides, and other constituents including steroidal and triterpenoid saponins, cyanogenetic glycosides, and anthraquinones. Important medicinal plants of the family are *Digitalis purpurea* (cardioactive), *D. lanata* (cardioactive), *Picrorhiza kurroa* (liver ailments), Verbascum *thapsus* (emollient, astringent, bronchial ailments), and Baccopa monnieria (brain and nerve tonic).

Solanaceae family includes herbs, shrubs, or small trees. The family is known for the presence of tropane, nicotine, and steroidal type of alkaloids. Important medicinal plants of the family are *Atropa belladonna* (pain relief, inflammatory conditions, antiemetic), *Datura stramonium* (spasmodic affections of the respiratory organs), *D metel* and *D innoxia* (hallucinogen, source of hyoscine, preoperative medication), *Hyoscyamus niger* (spasmolytic and anticholinergic properties; atropine is used in ophthalmology), *Hyoscyamus albus* (for treatment of asthma, bronchitis, and coughs), *Hyoscyamus muticus* (anesthetic), *Withania somniferum* (antioxidant, immunomodulatory), *Duboisi*a spp. (source of tropane alkaloids), *Solanum nigrm* (source of steroids, hepatoprotective), *Capsicum annum* (counter-irritant), and *Nicotiana tabacum* (source of nicotine; insecticide). *Nicotiana glauca*, tree tobacco, contains toxic alkaloid anabasine and nicotine, used as insecticide, as a poultice to treat swellings, bruises, cuts, wounds, boils, sores, etc.

Verbenaceae family contains three important medicinal plants such as *Verbena officinalis* (used for the treatment of cough, varicose veins, wounds, diabetes and to lower high body temperatures), *Vitex agnus-castus* (used to treat digestive ailments, stimulates progesterone production), and *Lantana camara*. It contains mucilage, an essential oil, and a glucoside called verbenalin.

Other families on Magnoliopsida that contain a very small number of medicinal plants include the following: Punicaceae: *Punica granatum* (antidiarrheic, dye); Rhamnaceae: *Rhamnus purshianus* (laxative); Zygophyllaceae: *Guaiacum officinale* (laxative and stimulant), *Peganum hanala* (headache); Iridaceae: *Crocus sativus* (against colds, hypnotic); Taxaceae: *Taxus baccata* (sedative, tranquilizer, cancer diseases); Balanitaceae: *Ballnites egyptia* (laxative, food oils, soap); Salvadoraceae: *Salvadora persica* (anti-inflammatory, dental cleaning); Scrophulariaceae: *Antirrhinum majus* (astringent, diuretic, and hemorrhoids); Phytolaccaceae: *Phytolacca* sp. (for the treatment of rheumatism and skin inflammation), etc.

The Orchidaceae is largest family in monocot by number of about 900 genera, 20,000-30,000 species and 70,000 hybrids. It is the most highly advanced family of the group. Members of this large and widespread plant family have colorful and fragrant blooms. The commercially important product is vanilla. Most vanilla is derived from *Vanilla planifolia*. The largest genera are *Bulbophyllum* (2000 species), *Epidendrum* (1500 species), *Dendrobium* (1400 species), and *Pleurothallis* (1000 species). Most of the species are epiphytic but some are terrestrial.

Orchids are an abundant treasure of alkaloids, flavonoids, glycosides, carbohydrates, and other phytochemicals. Different parts of Orchids are used for different therapeutic purposes, e.g., simple joint pain, acute rheumatism, tuberculosis, bone fracture, hyperacidity, eye trouble, stomach disorder, diarrhea, headache, pain killer, nervous disorder, blood purifier, etc. Orchids have been used as a source of medicine for millennia to treat different diseases and ailments including tuberculosis, paralysis, stomach disorders, chest pain, arthritis, syphilis, jaundice, cholera, acidity, eczema, tumor, piles, boils, inflammations, menstrual disorder, spermatorrhea, leucoderma, diarrhea, muscular pain, blood dysentery, hepatitis, dyspepsia, bone fractures, rheumatism, asthma, malaria, earache, sexually transmitted diseases, wounds, sores, etc., because of their incredible diversity, high alkaloids, glycosides, and other bioactive contents. Many orchidaceous preparations are used as emetic, purgative, aphrodisiac, vermifuge, bronchodilator, sex stimulator, contraceptive, cooling agent, and remedies in scorpion sting and snake bite. Various orchids are used for a variety of folk medicines and cures, e.g., *Bletia purpurea* (cures poisoning from fish), *Nervilia aragoana* (prevents sickness after childbirth), *Oberonia anceps* (poultice), *Spiranthes diuretica* (strong diuretic), *Catasetum* sp. (good for broken bones), *Anoectochilus* spp. (vegetable source), *Dendrobium salaccense* (cooked with rice), *Gastrodia* spp. (eaten like potatoes).

Some other medicinally important Orchids are *Acampe papillosa*, *Aerides multiflorum*, *Aeridesodoratum*, *Anoectochilus brevilabris*, *Arundina graminifolia*, *Calanthe sylvatica*, *Coelogynepunctulata*, *C. stricta*, *Cymbidium aloifolium*, *C. iridioides*, *C. longifolium*, *Gymnadenia orchidis*, *Dendrobium jenkinsii*, *D. amoenum*, *D. chrysanthum*, *D. chrysotoxum*, *D. densiflorum*, *D. fimbriatum*, *D. moschatum*, *D. nobile*, *Eria bambusifolia*, *E. pannea*, *Eulophia spectabilis*, *Geodorum densiflorum*, *Habenaria commelinifolia*, *H. furcifera*, *H. plantaginea*, *H. pectinata*, *Liparis odorata*, *Lusia trichorhiza*, *Malaxis muscifera*, *Nervilia aragoana*, *N. plicata*, *Oberonia caulescens*, *Papilionanthe teres*, *Phaius tankervilleae*, *Pholidota articulata*, *Vanda cristata*, *Rhynchostylis retusa*, *Satyrium nepalense,* and *Pleionemaculata*. Among these species, some are epiphytic and some are terrestrial.

Poaceae are the most economically important family and include all the true grains, the pasture grasses, sugar cane, and the bamboos. The majority members of Poaceae are cereals (rice, wheat, maize, etc.) and produce grain, source of starch. Many products from processed starch are used in pharmacy. Other medicinally important phytoconstituents of the members of Poaceae include saponins, alkaloids, sugars, silica, resins, bitter substances, essential oils, coumarins, carotenoids. The indole alkaloids—D-lysergic acid derivatives—isolated from ergot of infected rye are used as anticancer agents in some types of breast cancer. Plants belonging to the Poaceae family are also used in the treatment of gastrointestinal ailments, urinary tract diseases, benign prostate hyperplasia, sexual disorders, and aphrodisiacs.

Oryza sativa, source of staple food millions of Asian and African people, also possesses some medicinal properties (e.g., remedy for internal inflammation has a soothing and sedative effect, cures bowel problems, skin infection, scalds and burns, dysentery). *Eleusine indica* (plant decoction recommended for deworming, coughs, lung troubles, dysentery, heart problems, bladder and kidney stones, spleen

and liver complaints, and high blood pressure and also leaf as a poultice can be applied over sprains, dislocation of the bones, and pain in the lower back region). *Cynodon dactylon*, *Secale cereal,* and a few other plant species possess medicinal properties and a few others are important for essential oil, e.g., *Andropogon odoratus*, *Cymbopogon nardus*, *C. schoenonthus*, etc. Important medicinal plants of the Poaceae are *Agropyron repens* (laxative), *Arando donax*, *Cymbopogon citratus* (lemon grass), *Cymbopogon nardus,* and *Cymbopogon winterianus* (citronella grass), etc. (perfumes, antiworm).

Liliaceae family is composed of mostly herbs and rarely shrubs and contains a large number of plants with medicinal properties. Examples from this plant family include *Citrullus colocynthis* (laxative, skin diseases of cattle and domestic animals); *Collchicum autumnate* (sedative, anti-inflammatory); *Urginea 33ollusks* (cardiac ailments); and *Aloe vera* (healing of wounds, cosmetics). *Asphodelus aestivus*, *Asparagus racemosus*, *A. aphyllus*, *Drimia 33ollusks*, *Smilax aspera*, *Ruscus hypophyllum*, *Ruscus aculeatus*, *Muscari comosum*, *Lilium candidum*, *Hyacinthus orientalis*, *Allium cepa*, *A. sativum*, *Colchium cupani*, *C. luteum,* and *C. autunnale* are examples of few other medicinal plants of Liaceae.

Zingiberaceae members are annual or perennial rhizomatous herbs and are known for their medicinal values. The rhizome is sympodially branched and composed of distinct segments and are variously colored ranging from pale yellow, deep yellow, greenish blue, pink, or combinations in different species. *Alpinia calcarata*, *Amomum subulatum*, *Curcuma angustifolia*, *C. amada*, *C. zedoaria*, C. *longa*, *Elettaria cardamomum*, *Hedychium spicatum*, *Kaempferia rotunda*, *Zingiber officinale*, etc., are some of the important medicinal plant species of Zingiberaceae. They also provide many useful products for food, spices, dyes, perfume, etc. The Zingiberaceae plants are characterized by the presence of volatile oils and oleoresins. The rhizomes and fruits are aromatic, tonic, and stimulant. Some contain starch in large quantities and are used as food, while others yield an astringent and diaphoretic juice.

Other important families of Liliopsida are Typhaceae, Pandanaceae, Alimataceae, Hydrocharitaceae, Arecaceae, Araceae, Lamnaceae, Commelanaceae, Pontederaceae, Musaceae, Cannaceae, Iridaceae, etc.

6.3 Animal Phyla and Their Useful Products in Traditional Medicine

Zootherapy represents a strong evidence of the medicinal use of animal resources. Animal taxonomy is the grouping or categorizing of animals into different taxa in descending order as Kingdom, Phylum, Class, Order, Family, Genus, and Species. All animals are placed under the Kingdom Animalia; the Kingdom Animalia is divided into smaller groups, known as Phylum such as Porifera (sponges), Coelenterata or Cnideria (hydra, jellyfish, corals, anemones), Platyhelminthes

(flatworms), Aschelminthes (roundworms), Mollucs (chitons, tooth shells, clams, snails, squids), Annelida (segmented worms like earthworms, clam worms, leeches), Arthropoda (arthropods or joint footed organisms like horse shoe crabs, spiders, shrimps, centipedes, millipedes, insects), Echinodermata (sea lilies, starfishes, brittle stars, sea urchin, sea cucumbers (invertebrates); Hemichordata (acorn worms) and Chordata (chordates like sea squirts, lancelets, lampreys, sharks, bony fish, frogs, snakes, birds, mammals). The Phylum is further divided into even smaller groups, known as Classes (the Chordata Phylum splits up into different classes such as Agnatha—lampreys, Chondrichthyes—cartilaginous fish, Osteichthyes—bony fish, Amphibia—amphibians, Reptilia—reptiles, Aves—birds, Mammalia—mammals, etc.). Each Class is divided again into small groups, known as Orders (e.g., the Class Mammalia is divided into different Orders like Carnivora, Primate, Artiodactyla, Rodentia, etc.). The Order is divided into different Families on the basis of their similarities in characters (e.g., the Carnivora Order is splitted into families like Felidae–cats, Canidae–dogs, Ursidae–bears, Mustelidae–weasels, etc.). Every Family is divided into smaller Genus (e.g., the Felidae Family contains Genus Felis–domestic cats), Panthera-tigers, leopards, jaguars and lions and Puma-panthers and cougars, etc.), and then Genus into Species. Examples of taxonomic hierarchy for common jellyfish and tiger are given in Table 6.3.

The names of animals are in Latin and consist of two words (Binomial system). The first word in the name of an animal will be the genus, and the second name indicates the specific species.

A large number of products of pharmaceutical and medicinal importance are obtained from animal sources. Some of them are used as pharmaceutic excipients and others are used as important drugs or as nutritional supplements. The animal-based medicines come from different groups of domestic and wild animals under different classes and phyla including Oligochaeta (earthworms) and Hirudinea (leech) of Annelida phylum, Arachnida (spider) and Insecta (Spanish fly) of Arthropoda phylum, Amphibia (frogs), Reptilia (snakes), Aves (birds), and Mammalia (mammals) of Chordata phylum. These resources provide materials for the treatment of a wide range of common illnesses and injuries. The ethnozoological phenomenon is important, and the traditional knowledge on zootherapy may be helpful for the discovery of new sources of drugs. Out of the 252 essential chemicals selected by the World Health Organization, 11.1% have plant origins, while 8.7% come from animals (Marques 1997). Insects have proven to be very

Table 6.3 Different Taxa of animal kingdom in descending order with examples

Ranks of Taxa	Example (i)	Example (ii)
Phylum	Coelentarata	Chordata
Class	Scyphozoa	Mammalia
Order	Semaeostomeae	Carnivora
Family	Ulmaridae	Felidae
Genus	Aurelia	Panthera
Species	*Aurelia aurita* Linnaeus 1758	*Panthera tigris* Linnaeus 1758

important as sources of drugs for modern medicine since they have immunological, analgesic, antibacterial, diuretic, anesthetic, and antirheumatic properties (Yamakawa 1998). Andary et al. (1996) in a chemical screening of different insects confirmed the presence of proteins, terpenoids (triterpenoids and steroids, carotenoids, iridoids, tropolones), sugars, polyols and mucilages, saponins, polyphenolic glycosides, quinones, anthraquinone glycosides, cyanogenic glycosides, and alkaloids.

Drugs obtained from the faunistic sources are (i) whole animals, (ii) their organs, and (iii) glandular products (thyroid organ) and extract (liver), etc. Whole animals include European medicinal leech *Hirudo medicinalis*, Mexican medical leech *Hirudo manillensis* Indian species *Hirudinaria granulose*, American species *Macrobdella decora* and a few other *Hirudo* spp. (e.g., *H. michaelseni*, *H. nipponia*, *H. verbena*, *H. orientalis*) of Hirudinea. The beneficial effect of leeching occurs via blood decongestion and injection of several medicinally useful antithrombotic and anticoagulant bioactive molecules (e.g., hirudin, heparin) through their saliva. *Mylabris* sp. and *Lytta vesicatoria*—Spanish fly, the blistering beetles of Coleoptera, Insecta secrete a blistering agent, terpenoid cantharidin. Cantharides are skin irritants. Lac or shellac, the resinous substance, is prepared from a secretion of the insect—lac bug, *Laccifer lacca* Hemiptera, Insecta; musk scent, the dried secretion from the preputial follicles of the musk deer, *Moschus moschiferus*, Mammalia; civet, the secretion obtained from the perineal follicles of civet cats, Viverra civetta and other civet cats, Mammalia; chalk, finely powdered whitish or grayish rock, consists mainly of the shells of unicellular *Foraminifera animals*—member of a phylum or class of ameboid protists of kingdom Protista.

(ii) Skin of the African clawed frog *Xenopus laevis* of Pipidae family, Amphibia yields antibiotic peptides; skin extracts of the Ecuador poison frog *Ameere gabilinguis* of Dendrobatidae family, Amphibia contain potent analgesic compound epibatidine; pancreas of cow of Bovidae family and pig of Suidae family, Mammalia yields insulin, a peptide hormone; stomach, thyroid gland and liver of cow, of Bovidae family, Mammalia are sources of enzyme pepsin, hormone thyroxin, and liver extract and vit. B_{12}, respectively; cod-liver oil (source of vitamin A) is derived from *Gadus* spp., mainly from the Atlantic cod *G. morhua* of Actinopterygii under Oesteichthyes; menotrophin from postmenopausal woman urine, urokinase may be produced from human kidney cells (Homo sapiens of Hominidae family, Mammalia); antitoxins are used in medical practice in the form of antitoxic sera like antidiphtheria, antitetanus, antidysentery, antigangrene, antibotulinum, antiscarlatina, antivenom are produced by subcutaneous injection of a horse (or other animal) with toxins or anatoxins; antitoxin is thereupon formed in the blood serum of the horse, Equus caballus of Equidae family under Mammalia. Blood serum containing antitoxin is widely used in prophylaxis and treatment of diphtheria, tetanus, botulism, and other diseases, and it is also used for treatment of persons bitten by poisonous snakes.

Halibut (flat fish) liver oil (a very rich source of vitamin A, >50–100 times as rich as cod-liver oil) from *Hippoglossus vulgaris* (syn. *H. hippoglosus*, *H. americanus*, *Pleuronectes hippoglosus*), Atlantic halibut, of Pleuronectidae family,

Actinopterygii class; Pacific halibut is *Hippoglossus stenolepis.* Suet (the raw, hard fat or fatty tissue that grows or found around the loins and kidneys in cow, sheep—*Ovis aries*, goat—*Capra aegagrus hircus* of Bovidae family and other animals), lard (pig fat), spermaceti (wax found in the head cavities of the sperm whale—*Physeter macrocephalus* of Physeteidae family, Mammalia), wool fat (waxy substance, skin lipid, secreted by the domestic sheep *Ovis aries*),

(iii) Animal products and extracts include venoms and toxins from snakes (chordates of class Reptilia, order Squamata, family Pythonidae, genus Python and species Python reticulatus), spiders (arthropods of class Arachnida, order Araneae having ~114 families), scorpions (arthropods of class Arachnida, order Scorpiones), insects (arthropods of class Insecta, in total 26–29 living orders and many more families, genera and species), are polypeptides (α-bungarotoxin from cobras) or non-peptide toxins (tetrodotoxin from the puffer fish). They have been used as lead compounds in the development of novel drugs, e.g., teprotide, a peptide from the Brazilian viper, was the lead compound for the development of the antihypertensive agents cilazapril and captopril. Gelatin (obtained by the partial hydrolysis of collagen derived from the skin, white connective tissue and bones of animals like cow hide splits, bones, pork skin, and fish skin), honey (produced bees *Apis* spp.), beeswax (natural wax produced in the bee hive of honey by *Apis* spp.), chitin (most abundant natural amino polysaccharide, next to cellulose, derived from two marine crustaceans, shrimp-*Penaeus kerathurus* and crabs-*Carcinus mediterraneus* shells), chitosan—deacetylated chitin derivative, chondroitin sulfate (a sulfated glycosaminoglycan and an important structural component of cartilage and provides much of its resistance to compression, manufactured from cow cartilage), hyaluronic acid (non-sulfated glycosaminoglycan distributed throughout connective, epithelial, and neural tissues), animal (derived from cows, pigs pancreases and until the 1980s, animal insulin was the only treatment for insulin dependent diabetes), human chorionic gonadotropin—hCG (a hormone produced by the syncytiotrophoblast of the placenta following pregnancy of a woman), thyroxin (from sheep thyroid), pituitary gonadotropins (glycoprotein hormones secreted by gonadotrope cells of the anterior pituitary, used in fertility medication), heparin (an anticoagulant), vaccines (live attenuated viruses—rubella, measles, oral polio, mumps; or bacteria—bacillus calmette-guerin, BCG; inactivated viruses—parenteral polio, hepatitis A; or parts of the virus—pneumococcal vaccine, influenza; inactivated bacterial toxins—diphtheria and tetanus; genetically engineered—hepatitis B vaccine by inserting a segment of the viral gene in a yeast cell, sera (antidiphtheria, antitetanus sera from horse and sheep), etc.

In Ayurveda, CTM, and other traditional medicines as well as in folk medicine, products from animal resources (zootherapeutics) have been used for the treatment and relieve of different diseases many areas of the world since ancient times. These therapeutically useful animals belong to different plyla, family, genus, and species of the animal kingdom and include different species of Insecta like whole cockroach *Periplaneta americana* (for asthma), hind leg of cricket *Achaeta* sp. (as diuretic), whole house fly *Musca domestica* (for baldness, immature furuncles), whole leaf-cutting ant *Atta spp.* (for tendinitis), honey from different species of stingless

bee, e.g., *Tetragonisca sp.*, *Melipona sp.*, *Trigona spinipes*, etc. (for cataract, glaucoma, cough, throat inflammation, scutellum acne, influenza, stroke, and fortifier).

Arachnids include bird-eating spider *Theraphosidae* (in magic rituals), whole scorpion *Tytius sp.* (to treat its own sting); amphibians include whole toad *Bufo sp.* (for urinary retention), (to prevent oral diseases), hide (acne), venom (in magic rituals). Reptiles include whole lizard *Tropidurus torquatus* (in chicken pox), fat and also meat of neotropical rattlesnake *Crotalus durissus* (in rheumatism); fat of toad-headed turtle *Phrynops sp.* (in rheumatism), whole as well as blood of tortoise *Geochelone cf. carbonaria* (in erysipelas), heart (to stop the sensation of getting thirsty); birds such as fat of chicken *Gallus domesticus* (nasal congestion),white of the egg (to stop bleeding, dysentery), fat of greater rhea *Rhea americana* (in rheumatism), feathers (in stroke), feathers of ground-dove *Leptotila sp.* (in stroke), feathers of red-winged tinamou *Rhynchotus sp.* (in stroke), heart of southern lapwing *Vanellus chilensis* (to stay awake), freathers of tinamous *Crypturellus* sp. (in stroke), feathers of white-bellied nothura *Nothura boraquira* (in stroke), feathers of yellow-legged tinamou *Crypturellus noctivagus zabele* (in stroke); hide of the mammals like brocket deer *Mazama cf. americana* (in stroke), femur (to make a child walk sooner), hide of collared peccary *Tayassu tajacu* (in stroke), fecal material of Dog *Canis familiares* (in chicken pox), milk of donkey *Equus asinus* (in whooping cough), fat of fox *Dusicyon* sp. (in rheumatism), hide of giant anteater *Myrmecophaga tridactyla* (in stroke, fecal material of ox *Bos taurus* (to make mosquitoes go away) medulla (in baldness), penis (in sexual impotence), hide of porcupine *Coendou cf. prehensilis* (in stroke), fat of pig *Sus scrofa domesticus* (in furuncles, tumors), fat of sheep *Ovis aries* (torsion), hide of white-lipped peccary *Tayassu pecari* (in stroke), fresh manure of a dromedary *Camelus dromedaries* (to alleviate arthritis), the fats of the lion (*Panthera leo* (to alleviate abdominal pains), tusks of hippo *Hippopotamus amphibious* (as aphrodisiacs), fat from a manatee *Trichechus senegalensis* (to cure rheumatism, boils, and backache). The use of these animal products or zootherapeutics in traditional medicine largely exist outside of conventional medicine and may or may not be recognized as medicinally valuable in modern science.

6.4 Structural Organization of Drug Plants

Pharmacognostical standardization of herbal drugs includes macroscopic, microscopic, and physiochemical analysis in order to validate genuineness of the crude drugs of plant, mineral, and animal origin. Structural description of a drug plant at macroscopic (morphological) and microscopic (anatomical) levels is the first step toward establishing its botanical identity and purity, and it should be carried out before any chemical test (WHO 1998). Botanical identity of a medicinal plant may be ascertained by its structural characteristics, and accurate botanical identity ensures the quality of herbal preparation either in fresh, dried, or powdered state

(Springfield et al. 2005). Correct botanical identity based on the external morphology is possible when a complete plant specimen is available. Anatomical characters can help the identification when morphological features are indistinct (David et al. 2008). Anatomical perspective of drug plants is an integral component of pharmacognosy, especially while proposing diagnostic protocols for establishing the botanical identity and ascertaining the quality control of raw materials.

Materials used in herbal drugs are traded mostly as root, bark, twig, flower, leaves, fruit, and seed. For identification and authentication these materials, the availability of detailed morphological, anatomical, and pharmacognostic information is essential. Identification of active principles, wherever it is known, or a biologically active marker compound requires their standardization using appropriate chemical procedures such as TLC, HPLC, GLC, GC, quantitative TLC (QTLC), and high-performance TLC (HPTLC) can determine the homogeneity of a plant extract. Over-pressured layer chromatography (OPLC), infrared and UV–visible spectrometry, MS, GC, liquid chromatography (LC) used alone, or in combinations such as GC–MS and LC–MS, and nuclear magnetic resonance (NMR). Electrophoretic techniques, especially by hyphenated chromatographic techniques, are powerful tools, often used for standardization and to control the quality of both the raw material and the finished product. The results from these sophisticated techniques provide a chemical fingerprint as to the nature of chemicals or impurities present in the plant or extract (WHO 2002). Based on the concept of photo equivalence, the chromatographic fingerprints of herbal medicines can be used to address the issue of quality control.

6.4.1 Morphological Structure

At morphological structure level, the basic organization and form of drug plants and their organs are considered. Higher plants have three basic organs such as roots (e.g., tap root, fibrous), stems (e.g., solid, cylindrical, branched, unbranched), and leaves (e.g., simple, compound) in addition to flowers, fruits, seeds. Shape, size, and forms (e.g., herbaceous, woody, twining) as well as color, texture, fracture aspects, and characteristics of the cut surface of these major organs and associated other minor structures are also taken into consideration. Plant parts sorted and traded in the international market under different symbols and names include B = Bulbus (bulb); Cx = Cortex (outer layer, bark); Fl = Flos (flower); Fm = Folium (leaf); Fr = Fructus (fruit); Hb = Herba (greenery?); Ma = Medulla (inner layer, pith); Pc = Pericarpium (pericarp, peel, skin); Rml = (twig); Rx = Radix (root); Rz = Rhizoma (rhizome, tuber); and S = Semen (seed). Drugs are obtained from almost all forms of plants ranging from unicellular *Saccharomyces* or *Chlorella* to highly differentiated angiosperms *Azadiracta indica* or *Butea monosperma*. These diversified drugs and their sources were identified

formerly on the basis of their morphology. Morphological characters are not always reliable because many different closely related plants look similar in their external appearance. Internal structural characters or units of plants are taken into consideration for identification of plant drugs, especially when drugs are obtained in powdered, cut, or broken form.

6.4.2 Anatomical Structure

Internal structure could provide useful information in regard to correct identity and could help to differentiate one species from the closely related other species. Light microscopy is a common and effective method for the identification of pharmaceutically useful plants. Reliable anatomical descriptions of the medicinal plants and of possible adulterations provide a basis for fast identification and cheap purity controls of respective medicinal drugs by means of light microscopy. The importance of histological or anatomical characters of plant parts in their identification and detection of adulterants in them was first recognized in 1857 when Schleiden distinguished various types of *Sarsapharilla* roots on the basis of their endodermal cell characteristics. A good knowledge of cellular structures of various plant parts is therefore very essential for the purpose of quality control of plant drugs. Microscopic inspection of medicinal plant materials is indispensable for the identification of broken or powdered materials (WHO 1998). Microscopic examination (involving cells and tissues of the herbal products) can conveniently be employed for determining the presence of foreign adulterants or impurities. Microscopic analysis when used in association with other analytical methods provides invaluable evidences. Following the works of Metcalfe and Chalk (1950) and Metcalfe (1954), which today serve as standard references to plant anatomy, the use of vegetative anatomical characters in taxonomy has become a routine procedure (Jayeola 2009).

In anatomy, the study of cell, tissue and their organization in specific organs like root, stem, leaf, flower, fruit, seed in plants are considered. The embryo develops three fundamental (primary) tissues: protoderm, ground, and provascular. The protoderm develops into the epidermis of all three organs (root, stem, leaf). Epidermal cells undergo modification to develop various kinds of hairs, glands, guard cells, and waxy cuticles. The ground tissue is cellular filler that provides the bulk of the plant tissue between the epidermis and the vascular tissues. The ground tissues include the cortex and pith of stem and root, and the mesophyll of leaves. The provascular tissues mature into xylem and phloem, the conductive tissues in plants. The connections for these conductive tissues are continuous from root through stem to leaf. Much like the circulatory system in animals, no cell in the mature plant body is more than a few cells away from xylem and phloem.

6.4.3 Structural Organization of Plant Cell

The structure of different organs of a plant is made up of cellular units and, therefore, the crude plant drugs are made up of cells and tissues—the main seats of biochemical synthesis of all metabolites responsible for the vital life processes as well as pharmacological properties of crude drugs. A clear understanding of the structure, organization, and contents of these cells and tissues is important for meaningful study and correct botanical identification of crude drugs.

Cells vary in size and shape and they may be spherical, oval, polygonal, and rectangular or elongated. The average size of most cells, both animal and plant, varies from 1 to 100 μm and are thus visible only with the aid of a microscope. Cell component is divisible into three parts, e.g., cell wall, protoplasm, and vacuole. Cell wall is the outermost covering of the cell and protects the plant cell and gives it shape. Plant and animal cells are similar in all respects except the cell wall. This feature was lost in the distant past by the single-celled organisms that gave rise to the Kingdom Animalia. Plant cell contains plastids but not centrioles. Cell wall is composed of long chains of cellulose molecules embedded in a matrix of hemicellulose and pectin. Cell wall encloses the protoplasm and vacuole. Protoplasm is divisible into plasma membrane, cytoplasm, and nucleus. The outermost semi-permeable membrane surrounding the cytoplasm is called plasma membrane, which is made up of phospholipid bilayer impregnated with extrinsic and intrinsic glycoproteins. Intrinsic glycoproteins in plasma membranes include membrane transport carrier molecules and cell recognition antigens. Cytoplasm is a translucent mass of colloidal substances, composed of water, protein, carbohydrate, lipoids, and various organic and inorganic (ergastic or cell inclusions) substances. Cytoplasm is physically divisible into two parts, e.g., outer rigid and dense ectoplasm and inner thin fluidly endoplasm. There are no organelles in the ectoplasm. Nucleus, cell organelles, and ergastic substances are present in the endoplasm. The nucleus (center of transcription and replication of genetic material) is a round, oval or spherical structure and controls the development and function of the cell. It consists of outer double membrane bound covering, called nuclear envelope; nuclear sap, in which are present one or more nucleolus, nuclear ribosomes, and chromatin material (the genetic material made up of DNA). Organelles present in the endoplasm are endoplasmic reticulum (transport RNA from the nucleus and protein from ribosomes to the Golgi apparatus; plays role in lipid emulsification and digestion), ribosomes (translation sites of mRNA into protein, i.e., site of synthesis), Golgi complex (post office or packaging center for the cell, attaches address labels or functional groups to various cell products to direct them to their respective locations and ensure delivery), mitochondria (powerhouse of the cell), plastids (energy harvester), lysosomes (involved in apoptosis), peroxisomes (produce H_2O_2 metabolic by-product), etc. In addition, plant cell contains one or more vacuoles (cellular storage places, maintain turgor pressure and cellular immune function; help in endo- and exo-cytosis in animal cell) in the cytoplasm. Vacuole is surrounded by

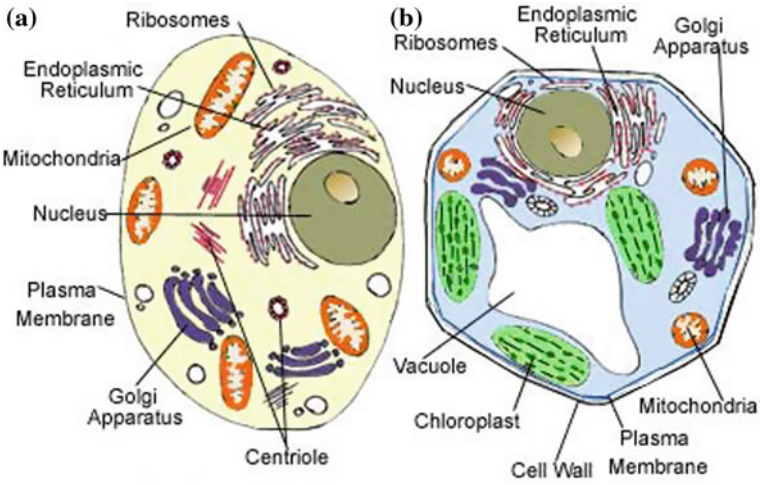


Fig. 6.1 Diagrammatic representation of **a** animal cell and **b** plant cell as may be seen under electron microscope. They are distinguished by the presence or absence of wall, chloroplast, and large vacuoles. Nucleus, cytoplasm, mitochondria, Golgi apparatus, endoplasmic reticulum, ribosomes, etc., are present in both the cells

protoplasmic membrane—the tonoplast and contains a number of inorganic ions, salts, and organic molecules. All these structural bodies are evident from Fig. 6.1.

The primary cell wall is a pervious flexible structure. This flexibility of the primary cell wall reduces gradually with age due to deposition of various hardening substances on its inner surface. This deposition process gives rise to different types of walls around cells of different plant organs. Chemical composition of the cell walls of various plant tissues often furnishes important chemo-microscopical characters, which can be used in the identification of plant drugs and detection of adulterants in them. The following types of cell wall are recognized in the plant cells.

6.4.4 Types of Cell Wall

6.4.4.1 Cellulosic Wall

The basic framework of the primary cell wall is composed of chains of cellulose molecules embedded in a matrix of mixtures of hemicellulose and pectic substances. Molecules of cellulose are made up of up to 300–2500 β (1 → 4) linked D-glucose units in straight chains. Cellulose cell walls can be recognized by the use of certain chemical reagents, e.g., solution of chlor-zinc-iodine gives a blue color with true cellulose. Ammoniacal solution of copper oxide (CUOXAM) dissolves

true cellulose, and the cellulose is precipitated when this alkaline liquid is poured into dilute sulfuric acid.

Hemicellulose (polyose) is a complex, branched, and heterogeneous polymeric network, based on pentoses (xylose, arabinose, and rhamnose), hexoses (glucose, mannose, and galactose), and sugar acids. It has a lower molecular weight than cellulose, forms the ground substance (matrix) of the primary cell wall along with pectin and connects lignin and cellulose fibers. Xylose is always the sugar monomer present in the largest amount, but mannuronic acid and galacturonic acid also tend to be present. In softwoods, however, mannose can be the most abundant sugar. A hemicellulose is present along with cellulose in almost all plant cell walls. While cellulose is crystalline, strong, and resistant to hydrolysis, hemicellulose has a random, amorphous structure with little strength. It is easily hydrolyzed by dilute acid or base as well as myriad hemicellulase enzymes. When treated with iodine solution hemicellulose gives a blue color. It dissolves in NaOH (17.5%) and KOH (24%) solutions and stains pink with Ruthenium red solution.

Pectin is a structural heteropolysaccharide (rich in galacturonic acid) contained in the primary cell wall of terrestrial plants. Pectic substances are amorphous carbohydrates and are usually methoxy derivatives. Pectin consists of a complex set of polysaccharides that are present in most primary cell walls and are particularly abundant in the non-woody parts of terrestrial plants. Pectin is a major component of the middle lamella, where it helps to bind cells together, but is also found in primary cell walls. They are hydrophillic in nature and maintain flexibility of the young cell wall. Like hemicellulose they are also soluble in the alkalis. They give blue color with methylene blue and yellow with chlor-zinc-iodine solution.

The amount, structure, and chemical composition of pectin differ among plants, within a plant over time, and in various parts of a plant. Pectin is an important cell wall polysaccharide that allows primary cell wall extension and plant growth. During fruit ripening, pectin is broken down by the enzymes pectinase and pectinesterase. In this process, the fruit becomes softer as the middle lamellae break down, and cells become separated from each other. A similar process of cell separation caused by the breakdown of pectin in the abscission zone of the petioles of deciduous plants happens at leaf fall. Pectin is a natural part of the human diet, but does not contribute significantly to nutrition. In human digestion, pectin binds to cholesterol in the gastrointestinal tract and slows glucose absorption by trapping carbohydrates. Pectin is thus a soluble dietary fiber. In medicine, pectin increases viscosity and volume of stool so that it is used against constipation and diarrhea.

As the cell matures, the cell wall looses its flexibility and secondary depositions of various chemical substances occur on the inner surface of the primary wall. These depositions result in the formation of a secondary cell wall, add mechanical strength to the primary wall, and modify its physical and chemical properties. The secondary cell walls consisted of 1–3 layers and are variously named as S_1, S_2, S_3, etc. (Fig. 6.2).

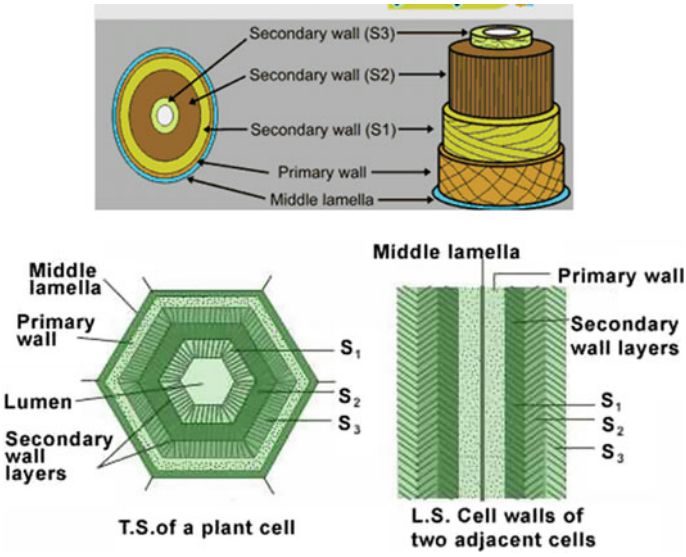


Fig. 6.2 Middle lamella, primary cell wall, and deposition of the layers of secondary cell wall—S_1, S_2, S_3 as seen in TS and LS of a plant cell wall

6.4.4.2 Lignified Cell Wall

When a cell wall is impregnated with lignin, it becomes a lignified cell wall. Cells with lignified walls are dead and constitute the mechanical and water conducting tissues such as trachcids, fibers, sclereids, and vessels. Lignin is a phenolic polymer made of phenylpropanoid units and functions to seal the secondary cell wall of plants. In the cell wall, it occurs chemically combined with hemicellulose. Lignified cell walls stain bright yellow when treated with aniline hydrochloride solution, permanent red with Safranin solution and yellow or deep brown with chlor-zinc-iodine. Treatment with phloroglucinol, followed by concentrated hydrochloric acid, stains lignified walls pink or reddish violet.

6.4.4.3 Cell Wall Containing Cutin, Suberin, and Waxes

The aerial surfaces of higher plants are covered with a continuous extracellular layer or coating on the epidermis consisting of cutin, suberin, and waxes. These coating materials are lipid in nature. Cutin is found on most aboveground parts; suberin is present on underground parts, woody stems, and healed wounds. Waxes are associated with both cutin and suberin. Cutin and suberin consist of oxidized and polymerized fatty acids and their esters. They differ from each other in the type of the acid, degree of esterification, and polymerization. Cutin is a principal constituent of the cuticle that coats the outer cell walls of the epidermis on the aerial

parts of all herbaceous plants. The cuticle is a three-layered structure, composed of a top coating of wax, a thick middle layer containing cutin embedded in wax, and a lower layer formed of cutin and wax blended with the cell wall substances pectin, cellulose, and other carbohydrates. Waxes are esters of long-chain aliphatic wax alcohols [CH_3 (CH_2) n CHOH (CH_2) m; n = 22–32] and corresponding fatty acids and they are extremely hydrophobic. Suberin is a polymer and is formed from hydroxy or epoxy fatty acids joined by ester linkages. Cutin, suberin, and their associated waxes are hydrophobic, form barriers between the plant and its environment, and protect plants from water loss, pathogenic infection and form a good thermal insulation of the cell wall. Aqueous sodium hydroxide solution (3%) dissolves and saponifies suberin, while methanolic potassium hydroxide solution (3%) dissolves and saponifies cutin. Both of them give red color with Sudan IV and Tincture of alkanna, and brown or yellow color with chlor-zinc-iodine.

6.4.4.4 Mucilaginous Wall

Mucilage is a polar glycoprotein and an exopolysaccharide or extracellular polysaccharides or polyuronides, formed from cellulose or pectic substances. Certain cell walls are sometimes adcrusted or covered with gums and mucilage. These substances possess slimy properties. Mucilage in plants plays a role in the storage of water and food, seed germination, and thickening membranes. Cacti (and other succulents) and flax seeds are rich sources of mucilage and contain mixtures of polysaccharides When treated with aqueous potassium hydroxide solution, mucilaginous cell walls swell. They stain blue or purple with chlor-zinc-iodine, pink with Ruthenium red, and red with Corallin soda.

6.4.4.5 Callose Wall

Callose is a polysaccharide in the form of β-1, 3-glucan with some β-1, 6-branches, and it exists in the cell walls of a wide variety of higher plants. Callose plays important roles during a variety of processes in plant development. It is laid down at plasmodesmata, at the cell plate during cytokinesis and during pollen development. It is produced in response to wounding and infection by pathogens. Callose is soluble in 5% alkali solutions and stains red with Corallin soda, and blue with Aniline blue. That forms a semitransparent horny substance and is a principal constituent of the exoskeleton, or outer covering, of insects.

6.4.4.6 Chitinous Wall

Chitin is a long carbohydrate polymer of a *N*-acetylglucosamine [$(C_8H_{13}O_5N)_n$], a derivative of glucose. It is related chemically to cellulose and occurs in the cell wall of fungi, exoskeletons of insects, crustaceans, arachnids, and other arthropods.

Chitinous cell walls give no reactions for cellulose or lignin. When heated with 50% potash at 160–170 °C for 1 h, chitin changes to chitosan, ammonia and acids. Chitosan gives a violet color when treated first with a 0.5% solution of iodine in potassium iodide and then with 1% sulfuric acid.

6.4.5 Plasma Membrane and Protoplasm

6.4.5.1 Plasma Membrane

Plasma membrane lies inside the cell wall and surrounds the protoplasm. It consists mainly of phospholipids matrix and proteins embedded in the matrix. Most of the membrane proteins are glycoproteins and they may be intrinsic (integral) and extrinsic (peripheral). Intrinsic proteins extend through the bilipid layer and among the fatty acid tails of the phospholipids. Peripheral proteins are loosely attached to either the interior or exterior surface of the plasma membrane. Other molecules present in the plasma membrane generally include cholesterol and glycolipids. Cell membranes are semi or selectively permeable to ions and organic molecules and controls the movement of substances in and out of cells. Plasma membrane contributes to cell adhesion, ion conductivity and cell signaling, and it serves as the attachment surface for the extracellular glycocalyx and cell wall and intracellular cytoskeleton. The fluid mosaic model of cell membrane and membrane components is shown in Fig. (6.3).

The proportion of protein, lipid, and carbohydrate in different biological membranes (in% of dry weight) vary considerably. The inner mitochondrial membrane contains the highest % of protein, and it was followed by the thylakoid membrane, nuclear envelope, Golgi complex, ER, and others. Lipid content was high in myelin, then mitochondrial outer membrane, RBC, and others. The relatively higher

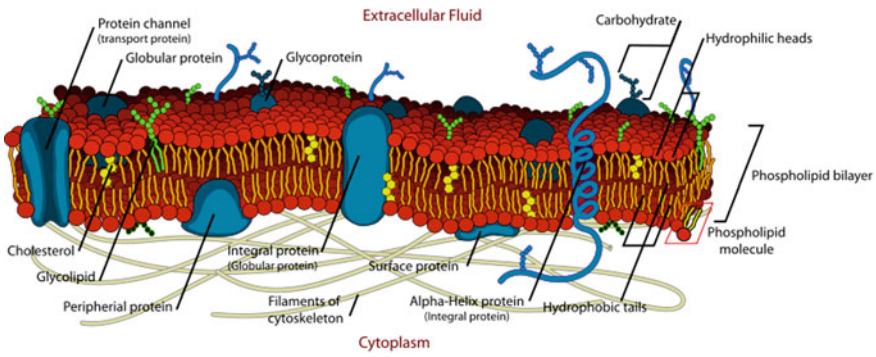


Fig. 6.3 Fluid Mosaic model of plasma membrane. *Source* Lady of Hats Mariana Ruiz, File, Cell membrane detailed diagram.svg

Table 6.4 Proportion of protein, lipid, and carbohydrate in different biological membranes expressed in% of dry weight

Protein, lipid, and carbohydrate of biological membranes, % of dry wt.				
Membranes		Protein	Lipid	Carbohydrate
Plasma membranes	RBC	49	43	8
	Liver cells	54	36	10
	Ameba	54	42	4
	Myelin	18	79	3
Nuclear envelope		66	32	2
Endoplasmic reticulum, ER		62	27	10
Golgi complex		64	26	10
Mitochondrion	Outer membrane	55	45	Trace
	Inner membrane	78	22	–
Thylakoid membrane		70	30	–

Sources Guidotti (1972) and Lotan, R. and Nicholson, G.L. in Advanced Cell Biology (ed.) by L.M. Schwartz and M.M. Azar. Van Nostrand (New York 1981)

% of carbohydrate was in liver cell membrane, ER, Golgi complex, RBC, etc. (Table 6.4).

The cytoskeleton of a cell is made up of microtubules (actin filaments, and intermediate filaments), supports cell shape and organization of cellular parts, and provides movement and cell division. The cytoskeleton is unique to eukaryotic cells. The endomembrane system is composed of the different membranes that are suspended in the cytoplasm within a eukaryotic cell. In prokaryotes, endomembranes are rare. The endomembrane system divides the cell into functional and structural compartments, or organelles and includes the nuclear membrane, the endoplasmic reticulum, the Golgi apparatus, lysosomes, vesicles, endosomes, the cell membrane, etc., but not the membranes of chloroplasts or mitochondria. The plasma membrane is also part of the endomembrane system. The system is consisted of a set of membranes that form a single functional and developmental unit, either being connected directly, or exchanging material through vesicle transport.

6.4.5.2 Protoplasm

The word protoplasm comes from two Greek words (*protos*-first, *plasma*-thing formed), first used in 1846 by Hugo von Mohl to describe the tough, slimy, granular, semi-fluid substance within plant cells, to distinguish this from the cell wall, cell nucleus, and the cell sap within the vacuole. Thomas Huxley later termed it as the physical basis of life but attempts for the creation of synthetic protoplasm in the laboratory were unsuccessful (Lazcano et al. 2008).

Protoplasm of a cell externally bounded by plasma membrane is known as protoplast. Protoplasm is the living content of a cell and is composed of a mixture of small molecules such as ions, amino acids, monosaccharides, and water, and

macromolecules such as nucleic acids, proteins, lipids, and polysaccharides. Protoplasm is distinct from non-living cell components, the ergastic substances, or inclusion bodies. In many plant cells, most of the volume of the cell is occupied by vacuole (bounded by tonoplast) and is divisible into cytoplasm and nucleus. All the contents of the cells of prokaryote organisms (which lack an organized nucleus) are contained within the cytoplasm. Within the cells of eukaryote organisms, the contents of the cell nucleus are separated from the cytoplasm and are then called the nucleoplasm.

Cytoplasm contains membrane bound (e.g., mitochondria, chloroplasts) and without membrane boundary (e.g., ribosome, centriole) different structural components, the cell organelles. An organelle is a specialized subunit within a cell that has a specific function and is usually separately enclosed within its own lipid bilayer. Eukaryotic and prokaryotic cells differ in their cell organelles content, relatively higher number of organelles is being found in the eukaryotic cell. Within

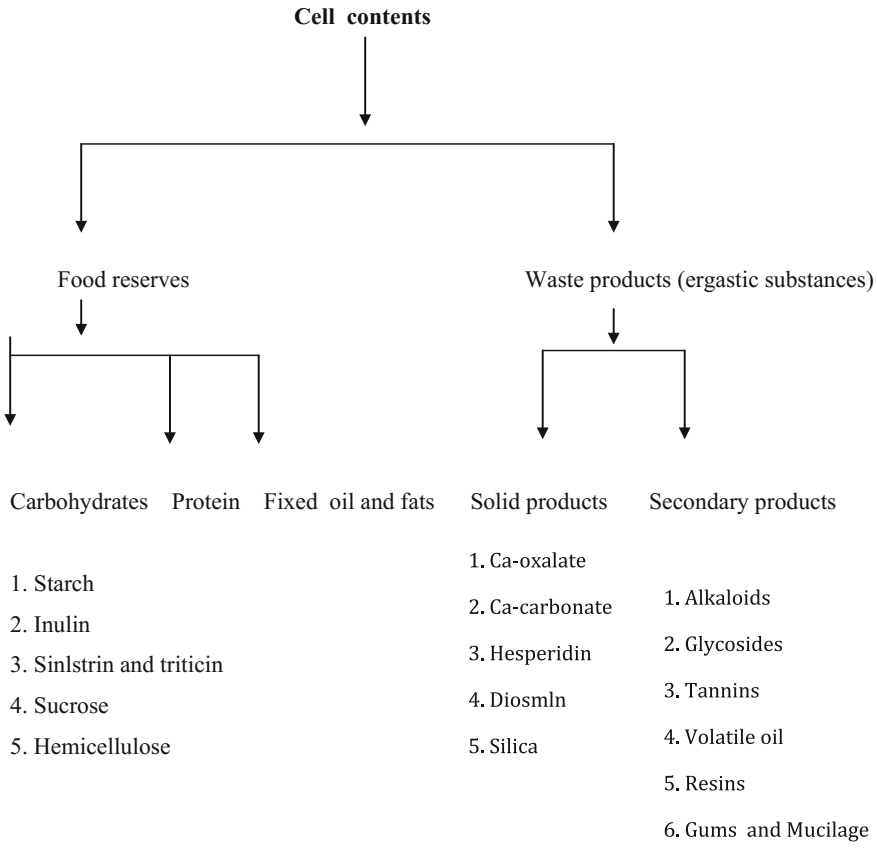


Fig. 6.4 Classification of cell contents: cell reserves or food substances and waste materials or ergastic substances

the cytoplasm, the major organelles and cellular structures include: (i) nucleolus, (ii) nucleus, (iii) ribosome, (iv) vesicle, (v) rough and smooth endoplasmic reticulum, (vi) Golgi apparatus, (vii) cytoskeleton, (viii) plastid, (ix) mitochondrion, (x) vacuole, (xi) cytosol, (xii) lysosome, (xiii) centriole.

Mitochondria and chloroplasts, which have double-membranes and their own DNA, are believed to have originated from incompletely consumed or invading prokaryotic organisms, which were adopted as a part of the invaded cell. This idea is supported in the Endosymbiotic theory. Classification of cell contents is shown in Fig. 6.4.

6.4.5.3 Cell Contents

Cell contents are of two types

(a) Cell reserves or food substances, and
(b) Waste materials or ergastic substances, secondary products

These are shown in Fig. 6.4.

6.4.5.4 Cell Reserves or Food Substances

1. **Carbohydrates**

Carbohydrate food reserves found in cells include starch, inulin, sinistrin, triticin, sucrose, and hemicelluloses, and different classes of carbohydrates are grouped into two classes such as non-sugars and sugars and are shown in Fig. 6.5.

Dietary carbohydrates includes

1. Sugars (digestible carbohydrate),
2. Fructo-oligosaccharides (non-digestible oligosaccharides, inulin),
3. Starch (digestible carbohydrate),
4. Cellulose (non-digestible carbohydrate).

1. Sugars include monosaccharides (glucose, fructose, and galactose) and disaccharides (sucrose, lactose, and maltose). These free sugars are highly water soluble and easily assimilated. Free sugars along with starches constitute a key source of energy;
2. Non-digestible oligosaccharides include inulin, a fructo-oligosaccharide;
3. Starch is a polysaccharide and basic to the human diet. It is found in abundance in cereals, roots, and tubers.
4. Cellulose is the indigestible component of carbohydrate with scarcely any nutritive value but contributes to dietary fiber.

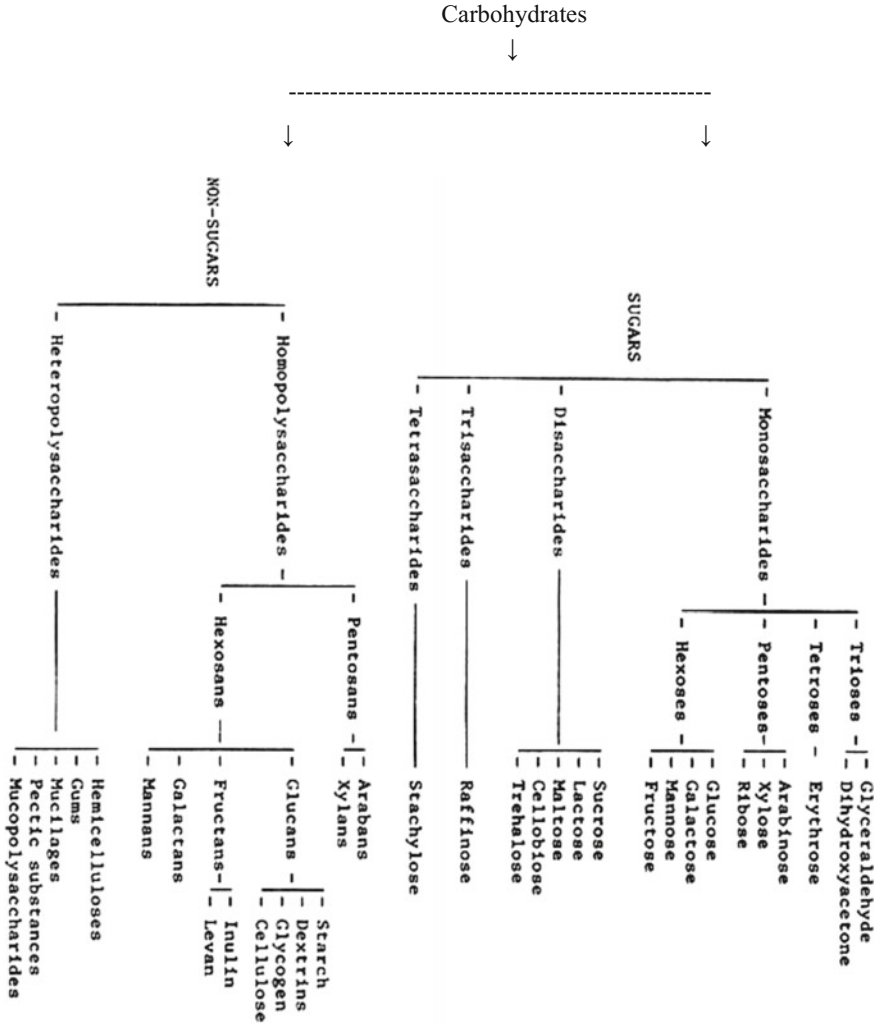


Fig. 6.5 Sugar and non-sugar carbohydrate food reserves found in cells

5. Dietary fiber is mainly non-starch polysaccharide. Two types of dietary fibers: insoluble cellulose and soluble non-cellulose polysaccharides. Insoluble fibers include cellulose, hemicellulose pectin, beta-glucans, hexoxane, pentoxane, lignin, and xanthan, and soluble fibers include storage polysaccharides like fructans, inulin, polyuronide, raffinose, xylose, pectin, gums, and mucilage. These are all degraded to a greater extent by the microflora in the human colon. The term fiber is something of a misnomer, since many types of so-called

dietary fiber are not actually fibrous; physiologically it is an important component of the diet and are found in vegetables, fruits, and grains.

6.4.5.5 Starch

Starch is the most common and widely distributed carbohydrate food reserve, which occurs in the form of grains or granules in the cells of most plant parts. Starch grains are often accumulated in large quantities in some underground plant organs such as potato tubers, cassava roots, yams, and ginger rhizomes. Cereal grains like rice, maize, wheat, and millet are full of starch grains, which constitute from 50 to 65% of their dry weight. Starch grains of different plants vary in size and shape and are characteristic of their sources. The size, shape, and structure of the starch grains from any particular plant vary only within definite limits. Starch grains may be spherical, oval, or polygonal in shape and occur as single grains, called simple grains or in groups of 2, 3, or more. When occur in groups, they are called compound grains and designated as 2-, 3-, 4-, or 5-compound, according to the number of grains forming the group. Thus, it is possible to distinguish between the starches derived from different sources (Fig. 6.6).

Morphological characters of starch grains under microscope are evident as hilum and striations. The hilum, which is not always distinguishable, is the part of the grain formed in the plastid. It appears as a point or slit or cleft in the central part or toward one end of the grain and is the starting point of formation of the grain. The

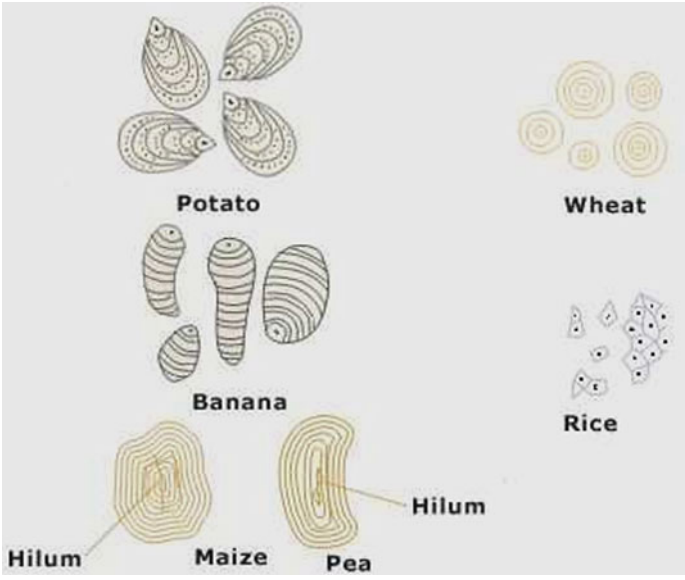


Fig. 6.6 Starches of rice, maize, potato, wheat, and pea

striations are eccentric or concentric rings, surrounding the hilum, formed by the deposition of successive layers of starch material as shell-like envelopes.

Chemically, starch consists of two closely related chains of α-D glucose polymers: strait chain amylose and branched chain amylopectin. Amylose is composed of 250–300 glucose units linked by 1 → 4 glycosidic bonds, while amylopectin is also composed of α-D glucose and linked by 1 → 4 glycosidic bond and additionally by 1 → 6 glycosidic bonds at every 25th glucose unit. Amylose is soluble in water while amylopectin is insoluble. This differential solubility of the components of the starch grains causes them to gelatinize when heated with water.

Starch grains constitute an important diagnostic character in the examination of powdered vegetable drugs. They are most abundant in drugs of underground structures and some seeds. Only occasional grains occur in most bark and wood drugs, and they are rare in leaf and flower drugs. Their shape and size also are characteristic of drugs of different origin. When treated with iodine solution, starch grains stain blue or blue-black.

6.4.5.6 Inulin, Sinistrin, and Triticin

Inulin is a polysaccharide food reserve. It consists of long chains of fructose units. Inulin either occurs in solution in the cell sap or as amorphous or sphaero-crystalline masses (Fig. 6.7). Some plants of the family Asteraceae and Campanulaceae contain inulin.

Sinistrin and triticin are closely related polysaccharides found in *Urgenea* and *Agropyron* species, respectively. Inulin is sparingly soluble in cold water but readily dissolves in water at 70 °C with gelatinization.

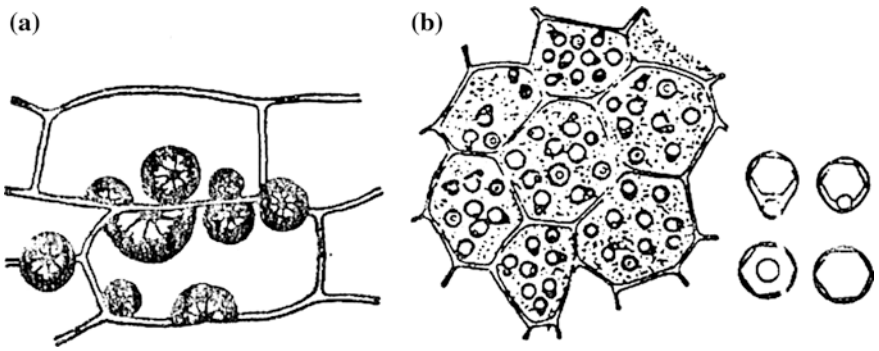


Fig. 6.7 **a** Inulin crystals in the tuberous root of Dahlia; **b** aleurone grains in the endosperm cells of Castor seed (Reconstructed from Dutta)

6.4.5.7 Sucrose

Sucrose occurs in high concentration in the cell sap of some plants, e.g., sugar cane and sugar beet. It is a disaccharide formed from glucose and fructose molecules. Sucrose gives a red precipitate when treated with Fehling's solutions after hydrolysis with dilute acids. It gives a deep red color when a few crystals of resorcin are added to a warm solution of sucrose in concentrated hydrochloric acid.

6.4.5.8 Hemicellulose

Hemicelluloses are heteropolysaccharides in the cell walls of terrestrial plants that have beta-(1 → 4)-linked backbones. Hemicelluloses include xylan, glucuronoxylan, arabinoxylan, mannans, glucomannan, and xyloglucans, and beta-(1 → 3, 1 → 4)-glucans. These polysaccharides contain many different sugar monomers, e.g., xylose, mannose, galactose, rhamnose, arabinose, and their acidified form (e.g., glucuronic acid and galacturonic acid). Beta-(1 → 3, 1 → 4)-glucans are restricted to Poales and a few other groups. Xylose is in most cases the sugar monomer present in the largest amount, although in softwoods mannose can be the most abundant sugar. Endosperm cells of *Nux-vomica* and date seeds contain hemicellulose in their walls. Ruthenium red solution stains hemicelluloses red.

6.4.5.9 Proteins

Proteins constitute food reserves of seeds and fruits. Storage protein occurs in the form of aleurone grains and also as amorphous masses. The aleurone grain consists of a mass of protein surrounded by a thin membrane. Often the protein mass encloses one or more rounded bodies or globoids and an angular body, called the crystalloid. Aleurone grains occur commonly in oil seeds, e.g., castor seed and linseed. For examining aleurone grains in them, the seeds should be treated with the following reagents after defatting.

(a) Millon's reagent, which stains the protein red on warming,
(b) Picric acid, which stains the crystalloid protein yellow.

Aleurone grains can be used as a means of identification of some seeds. For example, the endosperm cells of Nutmeg contain one large and several smaller aleurone grains. The larger one contains a large well-defined crystalloid. Endosperm and cotyledons of linseed contain aleurone grains with globoids, while some endosperm cells of fennel contain minute cluster crystals of calcium oxalate.

6.4.5.10 Fixed Oils and Fats

Fixed oils and fats, liquid and solid or semi-solid, respectively, at room temperature, are glycerol esters of fatty acids. They commonly occur with proteins as food reserves of oil seeds and fruits. Fixed oils occur as small highly refractive drops or droplets or globules and reserve fats occur in solid, colored, or crystalline masses. Feathery crystalline mass of fats occurs in the endosperm cells of Nutmeg. Oil globules associated with aleurone grains are common in linseed, castor seed, and *Nux-vomica* seed. Oils and fats are soluble in ether-alcohol. They are colored red brown or black with 1% solution of osmic acid, and red with Tincture of alkanna or Sudan red III and Sudan IV or Sudan red test reagents.

6.4.5.11 Waste Materials or Ergastic Substances

Many waste products of metabolism occur as cell contents in a number of plant drugs. These include: (a) solid substances like calcium oxalate and calcium carbonate crystals and silica, and (b) substances in solution in the cell sap, such as alkaloids, glycosides, volatile oils, resins, tannins, gums, and mucilage.

6.4.5.12 Solid Substances

Calcium Oxalate Crystals

Crystals of calcium oxalate occur commonly in the cells of many plant parts. They occur in various characteristic forms and shapes, e.g., prisms (single and twined), acicular crystals (single needle and raphides), rosettes, clusters, and microsphenoidal or sandy crystals (Fig. 6.8): Raphides are needle-shaped calcium oxalate crystals that are produced by higher plants for defense, calcium storage, and structural strength (Franceschi and Horner 1980; Franceschi and Nakata 2005; Nakata 2003).

Calcium oxalate crystals are of considerable diagnostic importance in the examination of plant drugs. Prisms of calcium oxalate occur in Senna, Liquorice, Cascara, Rauvolfia, Hyoscyamus, Quassia; rosettes in Stramonium, Senna, Rhubarb, Clove, Jalap; raphides (bundles of needles) in Coco-yam, Squill; single acicular crystals in Cinnamon, Gentian, Ipecacuanha, and microsphenoidal or sandy crystals in Belladonna. In certain instances, calcium oxalate crystals are also useful in distinguishing between the drugs of the same family. Typical examples are found in Solanaceous leaf drugs: Belladonna contains sandy crystals. Stramonium contains rosettes, and Hyoscyamus has single and twined prisms. They are also useful in the detection of adulterants. For example, presence of Phytolacca leaves in Belladonna samples can be detected by the acicular crystals of the former.

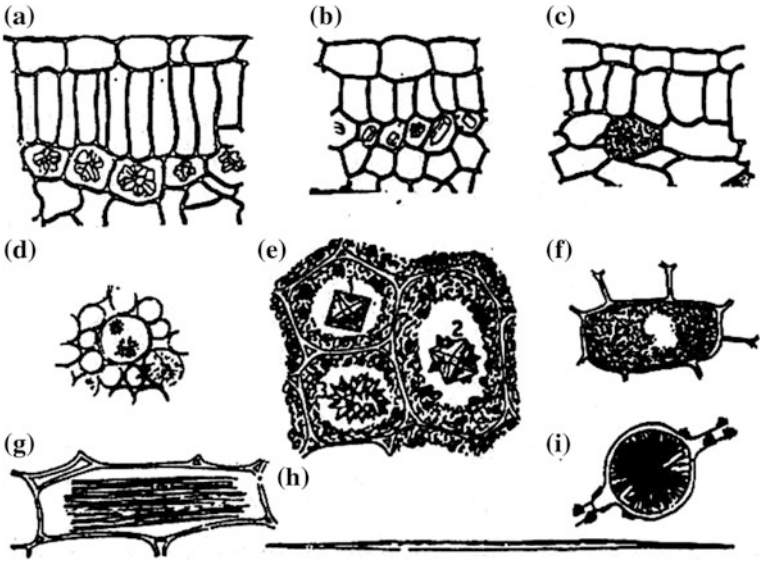


Fig. 6.8 Calcium oxalate crystals. **a** clusters in Stramonium; **b** prisms in Hyoscyamus; **c** microsphenoids in Belladonna; **d** rosettes in Senna; **e** (*1* and *2*), tetragonal crystals; **f** microcrystals in Cinchona; **g** raphides in Coco-yam; **h** acicular crystal in Squill; **i** sphaero crystal (Reconstructed from Trease & Evans and Hebert & Ellery)

Calcium Carbonate Crystals

These crystals are found embedded or incrusted in the cell walls of certain plants. Calcium carbonate crystals, in the form of cystoliths, occur in many plants of the families: Urticaceae, Moraceae, Cannabinaceae, Acanthaceae, and also in Combretaceae and Boraginaceae (Fig. 6.9a, b). Cannabis is a typical drug example that contains cystoliths of calcium carbonate in the epidermal cells of its leaves and the clothing hairs of its floral bracts. Calcium carbonate can be identified by the fact that it dissolves in acetic, hydrochloric, or sulfuric acid with effervescence.

The occurrence of cystolith hairs is an important criterion for the identification of marijuana leaf fragments. Cystolith hairs, however, occur among several dicotyledonous families, notably the Moraceae, Boraginaceae, Loasaceae, Ulmaceae, and Cannabinaceae (monocot). Since these develop in different forms in these families, marijuana can be differentiated in many cases. However, in other cases where similarity in cystolith development occurs, other morphological features, such as the trichomes on the other side of the leaf, are helpful in differentiation. In any event, cystolith hairs cannot be used as a sole criterion for marijuana identification (Thornton and Nakamura 1972)

Diosmin and Hesperidin Diosmin and hesperidin are two closely related flavonoids, which attract increasing interest for their biological properties and occur as feathery aggregates or sphaero-crystalline masses in cells of many plants of the family Rutaceae. An upper epidermal cell of Buchu leaves (*Barosma betulina*)

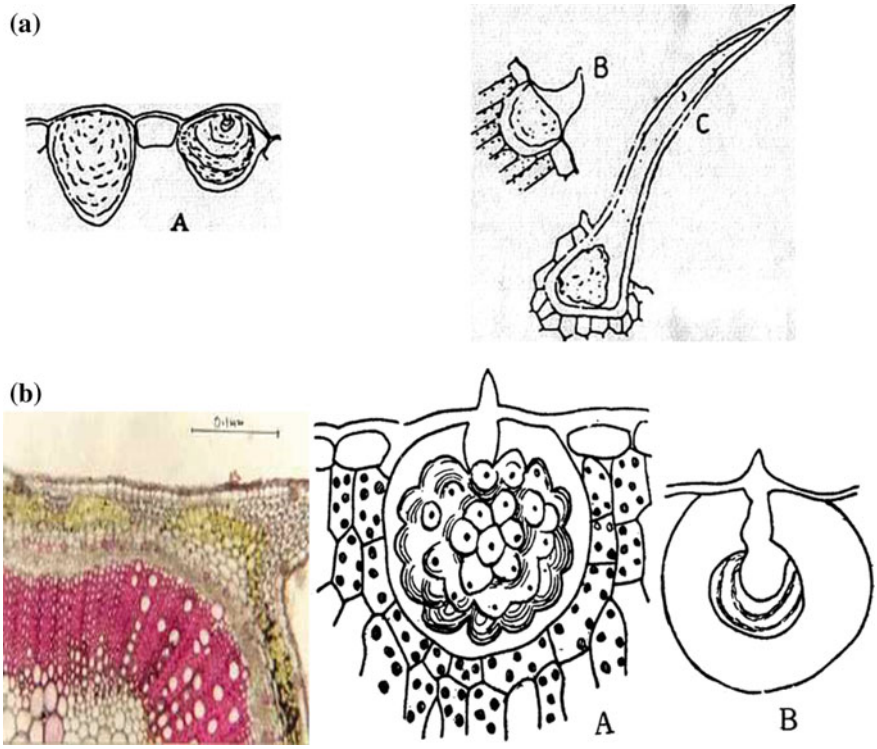


Fig. 6.9 **a** Cystoliths of calcium carbonate. A In epidermal cells of *Urtica dioica*; B In papillose epidermal cell of *Cannabis sativus* leaf; C In covering trichome of floral bract of *Cannabis sativus* (Reconstructed from Trease & Evans). **b** Cystoliths in epidermis

contains crystalline masses of diosmin, the major active constituent. Diosmin aglycone is diosmetin. Hesperidin is a flavanone glycoside found abundantly in citrus fruits (e.g., *Citrus aurantium*, *C. sinensis*). Its aglycone form is called hesperetin. Its name is derived from the word hesperidium, the kind of fruit produced by citrus trees. Crystals of hesperidin and diosmin are soluble in potassium hydroxide solution but insoluble in organic solvents. Diosmin is widely prescribed in Western Europe for varicose veins, heavy legs, venous insufficiency, premenstrual syndrome symptoms, and hemorrhoid crisis.

Although hesperidin and diosmin are not of common occurrence in plant drugs, their diagnostic importance in the identification and detection of adulterants in certain crude drugs cannot be overlooked. In fact, they have been serving as characteristic features of some important plant drugs.

Silica

Silica particles occur as incrustation on the cell walls, e.g., on the walls of epidermal cells of many grasses, or as masses in the interior of cells, e.g., in sclerenchymatous cells of cardamom seeds. Silica particles are insoluble in all acids

except hydrofluoric acid. The presence of silica in sections or powders of plant materials is not easily detected under the microscope. However, it may be examined by completely igniting the plant material and boiling the ash with dilute hydrochloric acid. The residue obtained after filtering the boiled mixture consists of the undissolved silica particles.

6.4.5.13 Substances in Solution in the Cell Sap

Alkaloids and Glycosides These are important therapeutically active chemical substances, which remain in solution in the cell sap of many plant drugs. Their presence can only be detected by treating extracts of the drugs with specific color reagents such as Dragendorff or Mayer's reagent for alkaloids, and Borntrager's reagent for anthraquinone glycosides.

Tannins Tannins are phenolic substances, which occur in solution in the cell sap. Presence of tannins in cells can be detected by treating extracts or sections of the drug with a dilute solution of ferric chloride when a bluish-black or greenish color is produced depending on the type of tannin present in the drug.

Essential Oils or Volatile Oils Essential oils or volatile oils are not oils in a strict sense, but often share with oils a poor solubility in water. They are the odorous principles of many drugs, which occur as droplets in the cells. Essential oils are highly complex mixtures of often hundreds of individual aroma compound (hydrocarbon molecules comprising of terpenes, alcohols, esters, aldehydes, ketones, and phenols). They are sparingly soluble in water, but soluble in alcohol. With osmic acid and Tincture of alkanna, they give similar reactions to those of fixed oils.

Resins The resin produced by most plants is a viscous liquid, composed mainly of volatile fluid terpenes, with lesser components of dissolved non-volatile solids which make resin thick and sticky. Resins occur as brown-colored irregular masses or in combination with volatile oils and gums in some specialized cells of many plant drugs. Examples of such drugs include Cannabis, Jalap, Capsicum, Ginger, and Podophyllum. Resins stain slowly with dilute Tincture of alkanna.

Gums and Mucilage These are polysaccharide complexes present or formed in cells of many plant parts, such as leaves, fruits, barks, and woods. Mucilage occurs in the leaves of Senna and Buchu and seeds of Linseed and Mustard and gums are produced in the woods of Acacia, Tragacanth, Sterculia, and Lannea (Jika) when they are naturally or artificially injured. Solutions of Ruthenium red, chlor-zinc-iodine and Methylene blue solutions stain gums and mucilage.

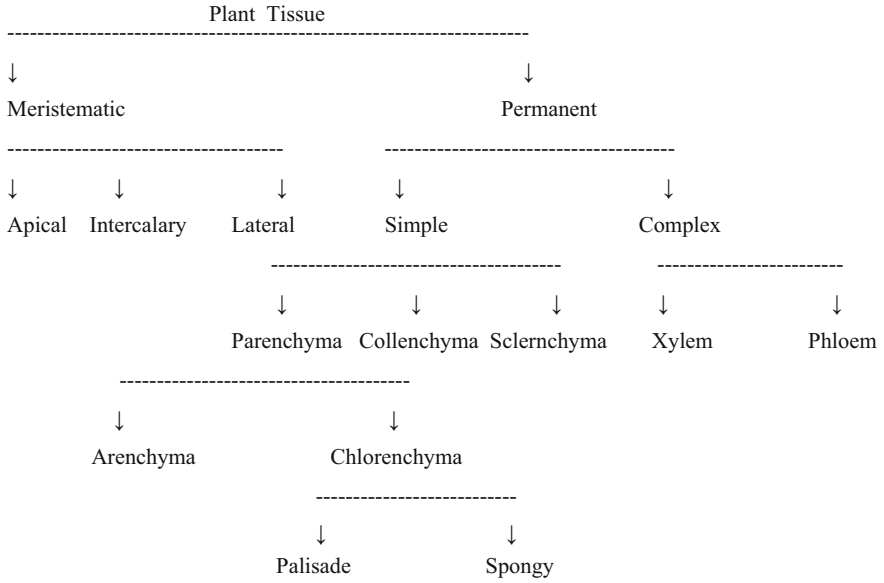


Fig. 6.10 Classification of plant tissues

6.4.6 Plant Tissues and Tissue Systems

As the cells continue to divide repeatedly to increase the size and volume of the plant seedling, they also undergo modification and differentiation in their form and structure to give rise to different groups of cells. These groups of cells, called tissues, constitute various organs and perform various functions in the plant. Plant cells on the basis of their structure and function are grouped into tissues. In higher plants, following classes of tissues are found (Fig. 6.10).

Structural organization of plant cells and tissues in the plant body from periphery toward center as may be evident clearly in T.S. or L.S. of a stem in the following order: epidermis (outer periphery or boundary layer) → cortex (middle zone in between periphery and central core zone) → pith (central core zone). The conducting tissues, xylem and phloem including cambium, lie in the cortical zone. Figure 6.11a, b shows this sort of arrangement.

Anatomical features or internal structures of drug plants are very useful in assigning the morphological groups of powdered, sectioned, broken, or mutilated crude drugs. They often offer important diagnostic characters for identification of both entire and powdered crude drugs and detection of adulterants in them. Thus, a good knowledge of plant anatomy and histology is essential for a person handling crude drugs.

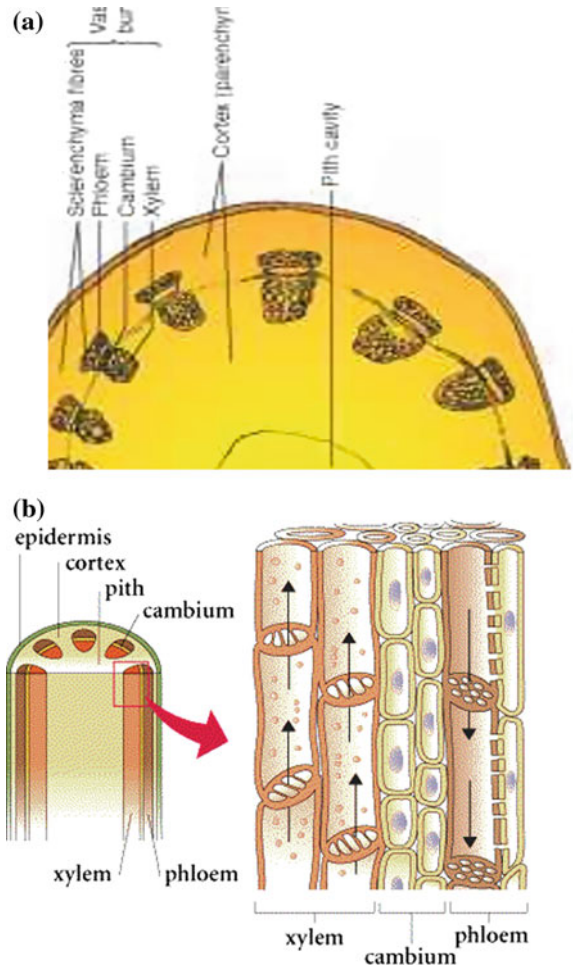


Fig. 6.11 **a** Transverse and **b** longitudinal sections of a dicot stem showing structural organization of plant cells and tissues in the plant body from periphery toward center as may be evident in the order: Epidermis (outer periphery or boundary layer) → Cortex (middle zone in between periphery and central core zone) → Pith (central core zone). Vascular tissues—xylem and phloem and also cambium lie in the cortical zone

6.4.6.1 Meristematic Tissue

Cells of the meristematic tissues are in a state of division or are capable of undergoing division, if and when needed and thereby support plant growth in volume. They are spherical, oval, or polygonal, having homogenous thin cellulosic walls, active cytoplasm, large nuclei, and smaller or no vacuoles.

6.4.6.2 Permanent Tissue

Permanent tissues are composed of cells, which have lost their meristematic property, i.e., their power of division, and have attained their definite form and size but provide structural integrity and sites for all physiological activities. Only under

certain conditions, they may become meristematic again, e.g., for the formation of cork cambium or cambium of the root or the interfascicular cambium of the stem. The cells of these tissues may be living or dead and thin walled or thick walled. Permanent tissues are formed by differentiation of the cells of the meristematic tissues and may be primary or secondary. The primary permanent tissues are derived from the apical meristems and the secondary permanent tissues from the lateral meristems. Permanent tissues are of three types: simple tissues, complex tissues, and secretary tissues.

6.4.6.3 Simple Tissue

A simple tissue is made up of one type of cells forming a homogenous mass and performing similar functions. On the basis of the structure of the cells and thickness of their walls, the following three types of simple tissues are recognized: parenchyma, collenchyma, and sclerenchyma.

The cells of parenchyma or parenchymatous tissue (Fig. 6.12a) are spherical, oval, or polygonal in shape with thinner cellulose walls and intercellular space between them. The parenchymatous tissues form the greater part of the plant body, particularly the softer parts are almost entirely composed of parenchyma. When a parenchymatous tissue contains chloroplast, it is called chlorenchyma, whose function is to manufacture food material.

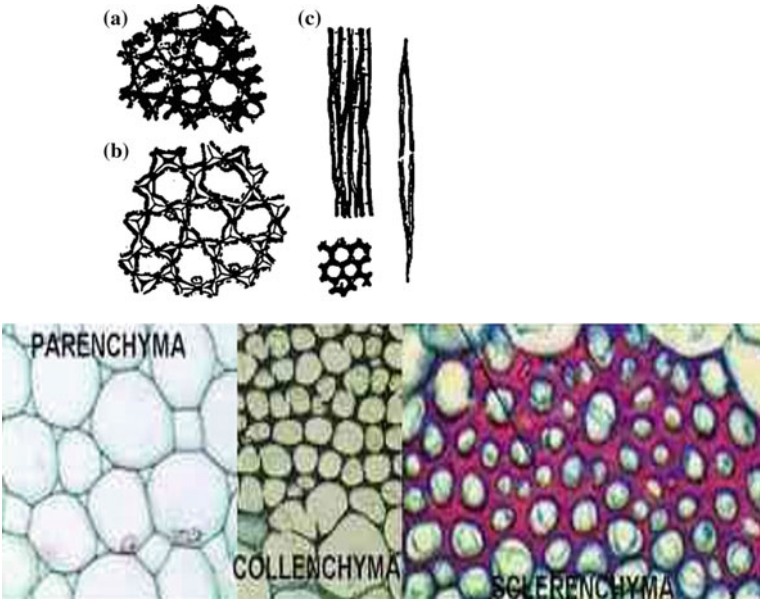


Fig. 6.12 **a** Parenchyma (t.s.); **b** collenchyma (t.s.); **c** sclerenchyma (L.S., T.S. and a single fiber) (Reconstructed from Dutta)

Collenchyma or collenchymatous tissue (Fig. 6.12b) is composed of somewhat elongated cells with oblique, rounded, or tapering ends. The cells are much thickened at the corners due to the deposition of cellulose impregnated with pectin. They look spherical, oval, or polygonal in transverse sections. The cell walls are soft, and they bear large simple pits on them. Collenchyma is found in the outer region of the stem, in the petioles and midribs of the leaves. It does not occur in the roots. Being flexible in nature, collenchyma tissue gives tensile strength to the growing organs.

Sclerenchyma or sclerenchymatous tissue (Fig. 6.12c) consists of long, narrow, and thick-walled cells, which are usually pointed at both ends and fiber-like in appearance. They are also called sclerenchymatous fibers or simply, fibers. Their walls are highly lignified and are provided with simple pits. They often become so thickened, due to excessive lignification, that the cavity or lumen of the fiber becomes very narrow or nearly obliterated. Sclerenchymatous cells are abundantly found in plants, and usually occur in patches or definite layers. Sometimes they also occur as single units among other cells. They are dead cells and serve purely a mechanical function, that is, they give strength, rigidity, flexibility, and elasticity to the plant body. Fibers vary greatly in their length. Plants like Jute, Cannabis, and Flax contain very long fibers. The fibers are of great economic value. They are used both in pharmaceutical and textile industries.

Sclereids or stone cells (Fig. 6.13) are special types of sclerenchymatous cells, which develop in some areas of the plant body to meet local mechanical needs.

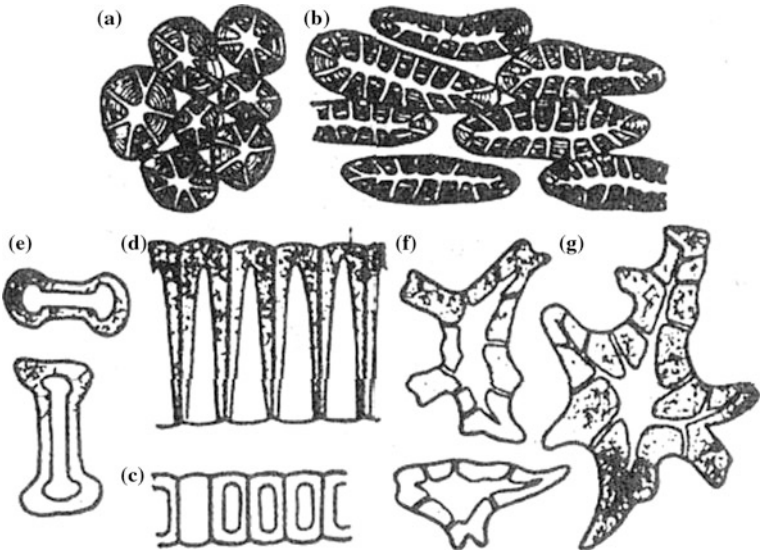
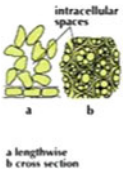
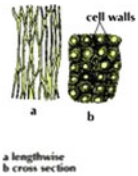
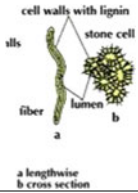


Fig. 6.13 Sclereids. **a**, **b** brachysclereids in pear flesh and coconut shell respectively; **c** and **d** macrosclereids in onion scale and seed coat of phaseotus; **e** osteosclereids in seed coat of Pea **f** and **g** astrosclereids in tea leaf and tsuga needles (Reproduced from Dutta)

Table 6.5 A synopsis on different simple tissues

Characteristics of different simple tissues			
Nature	Parenchyma	Collenchyma	Sclerenchyma
Cell structure in LS and TS as may be seen under microscope			
1. Shape (in T.S.)	Isodiametric, generally oval or spherical	Elongated	Angular
2. Cell wall	Thin, cellulose cell wall	Cell wall unevenly Thickened with cellulose at corners	Cell wall evenly Thickened with lignin
3. Nucleus	Nucleus present (living cell)	Nucleus present (living cell)	Nucleus absent (dead cell)
4. Vacuole	Single large vacuole	Small vacuole	Vacuole absent
5. Intercellular spaces	Space present	Generally absent	Absent
6. Occurrence	1. Cortex of root 2. Ground tissue in stem 3. Mesophyll of leaves	1. Below epidermis in stem 2. Generally absent in roots, leaves, and monocot stems 3. Absent	1. Stem 2. Veins of leaves 3. Hard covering of seeds, nuts
7. Function	1. Store food 2. Temporary support 3. Prepare food if chloroplast present	1. Provide mechanical support 2. Prepare food if chloroplast present (young dicot stem or herbaceous plants)	1. Fibers provide mechanical strength and lp n conduction when present in secondary xylem. Sclereids provide protection

Sclereids are very thick-walled, hard, and highly lignified sclerenchymatous cells. They do not have any definite shape, but are mostly isodiametric, polyhedral, short, cylindrical, slightly elongated, or irregular in shape with very narrow or no cell cavities. Their walls are provided with many simple pits. They contribute to the hardness of the plant part where they occur. They may occur in the cortex, pith and phloem of hard seeds, nuts and stony fruits and in the leaves and stems of many plants.

Sclereids may be broadly grouped into the following four types: (a) Brachysclereids or stone cells, which are more or less isodiametric in shape. They are commonly found, among masses of parenchyma, in the pith, cortex,

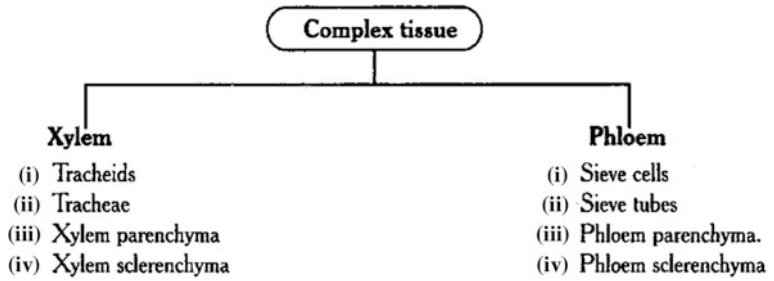


Fig. 6.14 Cellular components complex tissues

phloem and bark or many plants, pericarp of certain fruits, coconut shell, hard coverings of many seeds and fruits, etc. (b) Macrosclereids, which are rod-like sclereids with blunt ends. They are common in the bark, the seed coats of many leguminous seeds and the protective scales of onion and Garlic. (c) Osteosclereids, which are also rod-like sclereids, but they are dilated or lobed at one or both ends, somewhat like bones. They are commonly found in the seed coats and fruit walls, also in some leaves, (d) Astrosclereids, which are irregularly branched sclereids with radiating arms of various lengths, showing a stellate or star-like appearance. They are found in the leaves of Tea and Tsuga and barks of some Conifers. A synopsis on different simple tissues is given in Table 6.5.

Xylem and phloem are two major components of complex tissue. Each of this tissue is composed of a group of different cells (Fig. 6.14).

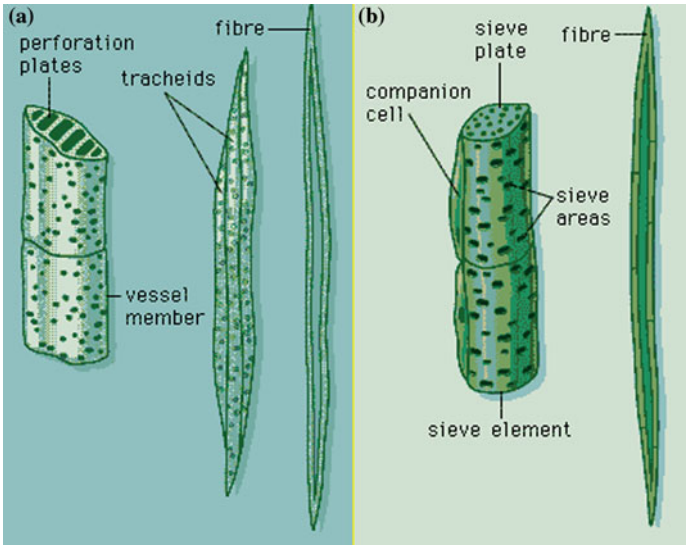


Fig. 6.15 Cellular components xylem (**a**) and phloem (**b**)

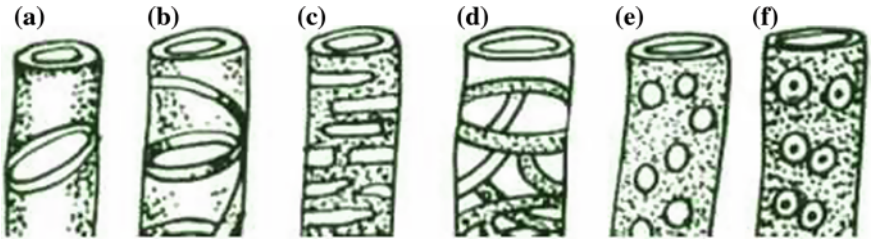


Fig. 6.16 The thickenings in the wall of tracheids are of different types such as **a** annular, **b** spiral, **c** reticulate, **d** scalariform, **e** simple pitted, and **f** border pitted

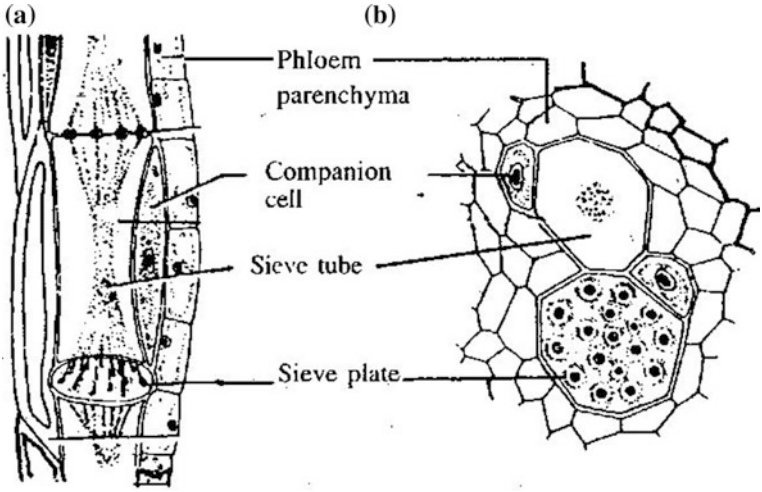


Fig. 6.17 Sieve-tube in longitudinal section (**a**); and in transverse section (**b**). Other components of the phloem tissue are also shown

Xylem and also phloem are composed four different types of cells. Cellular components of xylem are tracheid, trachea, xylem parenchyma and xylem sclerenchyma or fiber, whereas those of phloem are sieve tube, companion or sieve cell, phloem parenchyma and phloem sclerenchyma or fiber (Fig. 6.15). Xylem tissue is dead at maturity except its parenchyma component but only phloem sclerenchyma of phloem tissue is dead. Sieve tube becomes anucleated at its mature stage.

The tracheids are the fundamental components of xylem. Tracheids are unicellular, long, and cylindrical structures tapering at both ends. Their walls are highly lignified. Their thickenings are not uniform and form secondary layer of the cell wall. The thickenings in the wall are of different types such as (a) annular, (b) spiral, (c) reticulate, (d) scalariform, (e) pitted, (f) border pitted, etc. (Fig. 6.16).

Sieve tubes (Fig. 6.17) are slender, tube-like structures composed of elongated, thin-walled cells, placed end to end. Their transverse partition walls, perforated by a

large number of pores as in sieves, are called sieve plates. Although living, the sieve tubes do not posses any nucleus, but their cytoplasm is continuous through the pores of the sieve plate.

6.4.6.4 Importance of Phloem Anatomy in Pharmacognosy

Position of the phloem in the plant body often offers important anatomical characters in the microscopic examination of some plant drugs. Normally, in the stems of angiospermic plants, the phloem lies external to the xylem. But in some families of medicinal plants, such as Solanaceae, Apocynaceae, Myrtaceae, Convolvulaceae, Asteraceae, etc., a part of the primary phloem, called the intraxylary phloem, occurs internal to the primary xylem around the pith. Sometimes small groups of secondary phloem, called the interxylary phloem, are found embedded in the secondary xylem of some plants, such as *Strychnos nux-vomica*, *Combretum*, *Agave,* and *Aloe* species. In addition, occurrence of bast fibers is characteristic of some drugs (e.g., in the bark of *Cinchona* species).

6.4.7 Secretory Tissues and Cells

These tissues are composed of cells, which contain different kinds of secretion in them. Secretory tissues are of two types: glandular and laticiferous.

6.4.7.1 Glandular tissue

This tissue is composed of some special structures called glands, which contain some secretory or excretory products. Glands may consist of single isolated cells or small groups of cells with or without a central cavity. They may occur as external glands on the epidermis or as internal glands embedded in other tissues of the plant body. Cells of these glands are parenchymatous and contain abundant protoplasm with large nuclei.

External glands occur on the epidermis of many plants in the following forms (a) water secreting hairs, also known as hydathodes; (b) glandular hairs containing gummy or irritating poisonous substances as in *Nicotiana* (tobacco), *Plumbago*, etc. (c) nectar secreting glands as in carnivorous plants (Fig. 6.18).

Internal glands (lysigenous, schizogenous, and laticifers) are of the following types: (a) oil glands, which secrete volatile or essential oils, as in the leaves and fruits of orange and lemon; (b) mucilage glands, as in the leaves of *Piper betle*; (c) gum, resin, or tannin secreting glands, e.g., resin ducts of *Pinus palustris*, (d) digestive glands secreting enzymes, as in the leaves of *Digitalis purpurea*, and (e) water secreting glands, also called hydathodes, as in leaves of water lettuce.

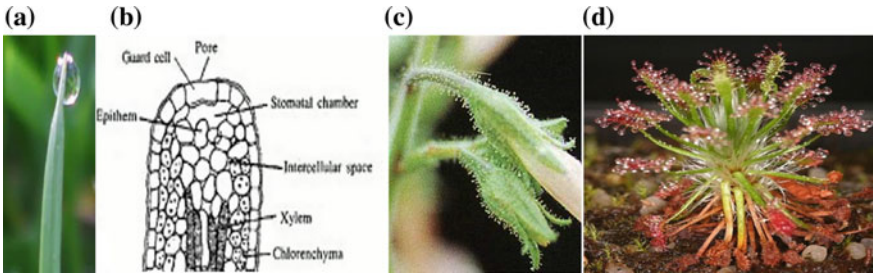


Fig. 6.18 Hydathodes. **a** a grass leaf showing exudates through hydathode; **b** v.s. of leaf through hydathode. Epithem-loosely arranged parenchyma with few/no chloroplasts; **c** glandular hairs containing gummy or irritating poisonous substances as in *Nicotiana*; **d** nectar secreting glands as in carnivorous plants as found in narrow-leaved Sundew (*Drocera*)

Importance Glandular Tissue in Pharmacognosy

Glands are of pharmacognostical significance in the examination and identification of certain crude drugs. Glandular tissues in plants produce a wide variety of important metabolites like gums, resins, volatile oils, nectar, latex, and other substances of pharmacognostical importance.

6.4.7.2 Laticiferous Tissue (Fig. 6.19)

This tissue consists of thin-walled, elongated, and much-branched cells or ducts, which contain a milky or colorless juice known as latex. Latex as found in nature is a milky fluid found in 10% of all flowering plants (angiosperms). It is a complex emulsion consisting of proteins, alkaloids, starches, sugars, oils, tannins, resins, and gums that coagulates on exposure to air. The cells of this tissue contain a thin layer of protoplasm lining the cell wall and numerous nuclei. Laticiferous tissue is irregularly distributed in the mass of parenchymatous cells of the various plant organs. They are of two kinds: **b**. latex cells, and **c**. latex vessels.

(a) **Latex vessels**: They are formed from rows of elongated meristematic cells by the dissolution of their transverse partition walls. Many such vessels develop almost parallel to each other and extend sideways forming branches in the same way. In the mature portions of the plant, these independent vessels join with each other by the fusion if their branches forming a network. Latex vessels are characteristic of the Opium poppy plant (*Papaver somnifemm*) the latex present in the latex vessels of its capsule produce the famous narcotic analgesic drug Opium.

(b) **Latex cells**: Latex cells are also elongated and much-branched cells, which look apparently similar to the latex vessels. But they are single independent cells, which originate as minute structures and then elongate and branch with the growth and development of the plant, but their branches do not fuse

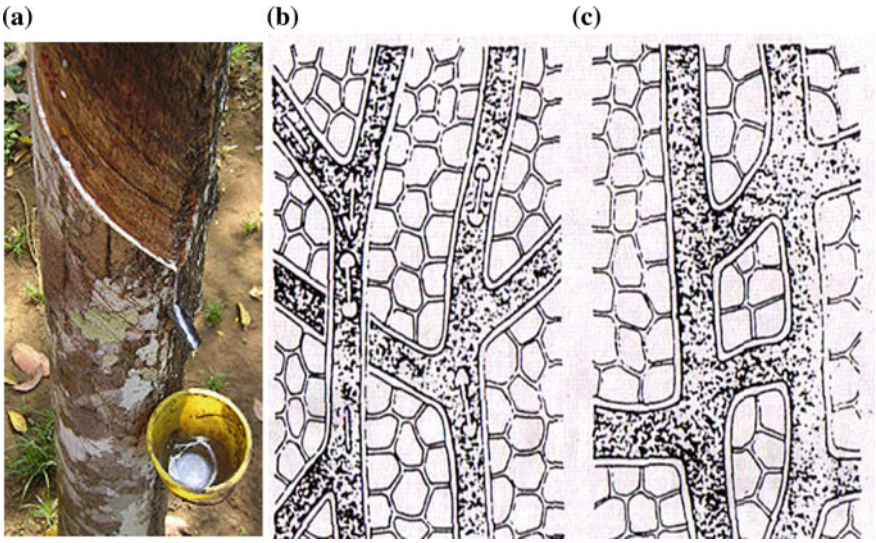


Fig. 6.19 Laticiferous tissue. **a** Latex from a robber tree through latex cells; **b** latex cells; **c** latex vessels

together (as in case of the vessels) to form a network. Latex cells are found in the leaves and stems of *Calotropis* sp., *Catharanthus roseus*, *Euphorbia* sp., *Thevatia* sp. and young fruits of *Carica papaya* and those of many other plants. All these varied tissues aggregate together and get arranged in some form or the other to constitute a number of tissue systems which form the structures of various plant organs. A tissue system may be defined as a collection of tissues, either of the same or of different types, which have the same origin, and which perform a common or similar function. Based on the type of function and position, plant tissues are grouped into three systems such as (a) Epidermal tissue system—constitutes the epidermis or outer covering of various plant organs, (b) Ground or Fundamental tissue system—constitutes the major part of the plant body, and (c) Vascular tissue system—forms the vascular bundles present in the stele region of the stems and roots.

6.5 Drugs from Whole Plant

Beside the different organs, the whole plants (herbs and shrubs) are also trades in the international market. Among many others, this item includes *Andrographis paniculata*, *Bacopa monnieri* and *Bacopa floribunda*, *Centella asiatica*, *Datura inoxia*, *D. metel* and *D. stramonium*, *Ephedrasinica*, *Catharanthus roseus*, *Claviceps purpurea*, *Saccharomycescerevisiae,* etc.

6.5.1 Structure of Organized Drugs

Organized drugs contain cellular structure and are comprised of whole plant (herb) or plant parts such as leaf, flower, fruit, seed, bark, wood, root, rhizome, etc.

6.5.2 Leaf Morphology

Leaves are flattened lateral outgrowths of the stem, generally green in color and form the foliage of a plant. A typical leaf (Fig. 6.20) consists of two main parts, an expanded blade or lamina and a stalk or petiole. Petiole is absent in sessile leaf, and leaf with petiole is called a petiolate leaf. Leaves of different monocot and dicot plants differ in shape, size, and orientation. The way a leaf looks in terms of leaf shape, leaf margin, leaf arrangement, and leaf venation is important for identifying plants of interest. These structures are always species specific and will consistently grow to a genetically determined pattern and shape.

Leaf characteristics, e.g., size, shape, margin, hairs base, apex, stomata, venation, and palisade ratio are important for identifying plant species. Unlike stems or roots, leaves are determinant in growth activities; they grow and achieve a specific pattern and shape, then stop. Other plant parts like stems and roots usually continue to grow as long as they have the resources to do so. Leaves of different plant species are different as ferns have fronds; conifer leaves are typically needle or scale-shaped; angiosperm leaves of standard form include stipules, a petiole, and a lamina; lycophytes have microphyll leaves; grasses have sheath leaves and other may have specialized leaves (e.g., drocera, nepenthes). Flattened chlorophyllous leaf-like structures of non-vascular plants, Bryophytes (i.e., liverworts and mosses), are not

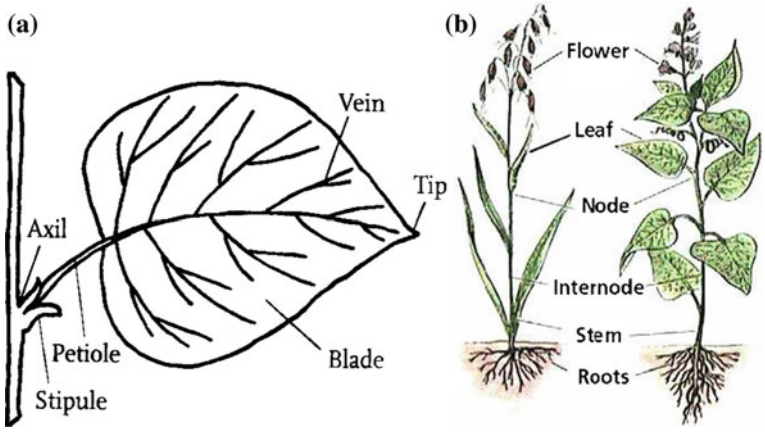


Fig. 6.20 **a** Representive of a dicot leaf, **b** monocot and dicot leaves with respective plant

considered true leaves by all botanists since they lack vascular tissue. Vascularized true leaves, the euphylls, are found in ferns, gymnosperms, and angiosperms. Euphylls are also referred to as macrophylls, megaphylls, or large leaves.

6.5.2.1 External Structure of a Leaf Bears the Following Parts

Axil: The leaf axil is where the petiole of the leaf attaches to the stem.
Leaf blade: The broad expanded region of the leaf. The broader the leaf, the greater the surface area exposed to sunlight… which leads to a higher rate of photosynthesis.
Petiole: The leaf's petiole is a thin short stalk that attaches the leaf blade to the stem.
Stipule: A leaf's stipule is a leafy outgrowth on either side of the leafstalk or petiole. It exhibits no specific function.
Tip: The leaf tip or leaf apex is the terminal point of the leaf.
Vein: The veins are the vascular tissue, made up of xylem and phloem, and are located in the spongy layer of the mesophyll. The pattern of ramification of the veins is called venation. Leaf venation may be reticulate, if net-like ramification as in case of the dicot leaf or parallel, if veins run parallely end to end through the lamina as in case of monocot leaf.
Midrib: The main strand of vascular tissue that runs centrally through the lamina from base to apex is called the midrib.
Leaf margin: The edges of the leaf lamina are called the margins.
Lamina base and apex: The point at which the margins meet the petiole is called the lamina base, and the tip of the lamina is known as the apex.

The shape of lamina, type of its margin, apex, and base vary from plant to plant. These variations constitute important morphological characters for identification and differentiation of leaves of different drug plants. For example, Belladonna (simple dull green ovate leaves with acute apex, hairy, grow in pairs, one leaf being half as large as the other), Buchu (leaf simple, entire, obovate, margin dentate in the upper two-thirds of the leaf and serrate toward the base, strong aromatic odor); Coca (leaf entire, oval-elliptical, broad, greenish-brown or clear brown, smooth, slightly glossy and coriaceous, midrib prominent underneath, areolated); Digitalis (leaf simple, entire with dentate margin, arranged spirally to form tight rosette, covered with gray-white pubescent and glandular hairs, imparting a woolly texture); Eucalyptus (leaf evergreen broad lanceolate shape, prominent midrib, covered with oil glands, older leaf with a red band along its edge, surface glossy or glaucous), Gymnema (opposite, elliptic or ovate to ovate, apex obtusely acute, base truncate or obtuse, subcoriaceous, densely tomentose below), Hamamelis (leaf alternate, simple, obovate, elliptic (oval), margin sinuate/undulate, undulate, venation: pinnate, deciduous); Hyoscyamus (*Synonym* Henbane, leaves are ovate-oblong in shape, sinuate-dentate, or coarsely dentate in outline, and acute at the apex, pale green in color, and clothed on both sides with long soft hairs, many of which secrete a resin,

which renders the leaves clammy and sticky to the touch; midrib broad and conspicuous), Mint/Spearmint (leaf simple, entire, oblong to lanceolate with a blunt tip, margin serrated, arranged in opposite pairs, saw tooth shape and a striking menthol smell), Senna (the leaves are pinnately compound with opposite paired leaflets), Squill (rosetted leaves from bulbous plant, basal, lanceolate to linear-lanceolate, glabrous with smooth margin); Stramonium (leaves are large and angular, ovate, acute, acuminate, uneven at the base, with a wavy and coarsely-toothed margin, and branching veins very plainly developed); Tea (leaf hard, thick and leathery; surface matt, marginal veins indistinct and appear sunken in lamina blade elliptic with obtuse or broadly obtuse apex; base cuneate, margin bluntly serrulate to sinuate-serrulate with more or less incurved teeth, glabrous above and villose below when young, becoming sparsely villose as the leaf ages leading to glabrous); Tulsi (leaves simple petiolate, entire, ovate, hairy, usually slightly toothed, with characteristic strong aroma), and Vasaka (leaves are elliptic-lanceolate or ovate-lanceolate, entire, hairy, light green above, dark below and leathery), all of which are leaf drugs, can easily be distinguished from each other by using these characters. Morphological characters form the main basis of identification when the drugs are composed of entire leaves.

6.5.2.2 Simple and Compound Leaf

Leaf may be simple or compound (Fig. 6.21). Leaf containing single lamina and auxiliary bud at its axis is called simple leaf. Lamina may be entire or if dissected from the margin but notch is incomplete. In a simple leaf margin may be entire (e.g., mango, tobacco), lobed (e.g., ginkgo, cotton), or incised not up to midrib or rachis (e.g., belladonna, datura, castor). In a compound leaf, lamina is divided into independent leaflets, and notch is completed and reaches to the tip of the petiole is

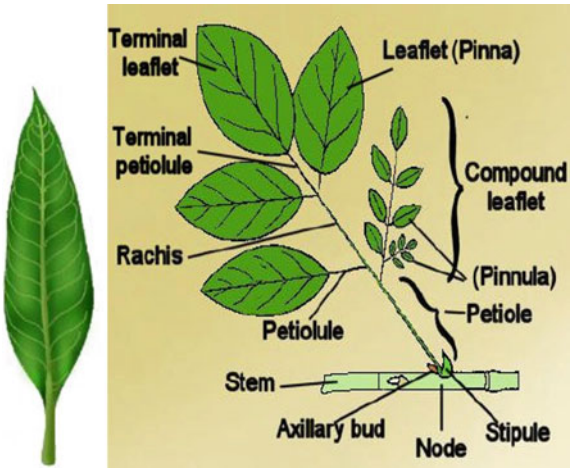


Fig. 6.21 Simple leaf and different parts of imparipinnate compound leaf

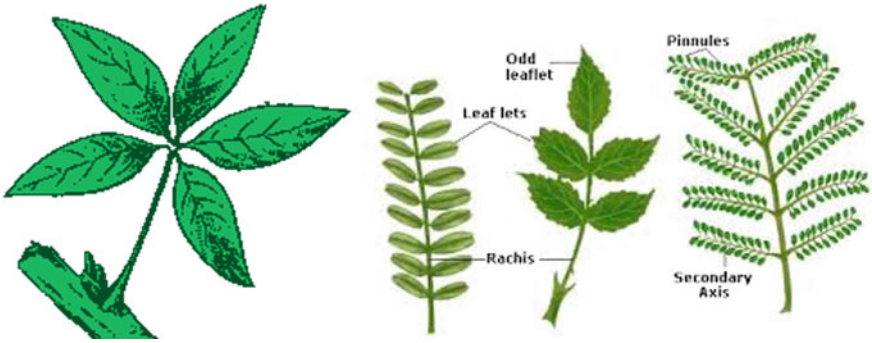


Fig. 6.22 Palmate, paripinnate, imparipinnate, and bipinnate compound leaf

called compound leaf. It does not contain auxiliary bud (e.g., rose, coriander, neem). There are two types of compound leaves, viz. palmate and pinnate with imparipinnate and paripinnate variations (Fig. 6.22).

Compound leaves are a characteristic of some families of higher plants, such as the Fabaceae (*Cassia* and *Tamarindus* species). Palmately compound leaves have the leaflets radiating from the end of the petiole, like fingers off the palm of a hand (e.g., *Cannabis*, *Aesculus*); palmately compound leaf is unifoliate when single leaf let is at the tip of the petiole (e.g., lemon); bifoliate when two leaf lets are on the tip of the petiole (e.g., Balanites); trifoliolate when there are just three leaflets (e.g., clover, laburnum); multifoliate many leaf lets are on the tip of the petiole (e.g., *Bombax*); pinnately compound leaves have the leaflets arranged along the midrib; imparipinnate bears a terminal leaflet (e.g., *Fraxinus*); paripinnate lacks a terminal leaflet (e.g., *Swietenia*); there may be unipinnate if leaflet is present on the main midrib (e.g., *Cassia*); bipinnate or twice pinnate if leaflets are present on the secondary branches (e.g., *Acacia*) and multipinnate if many leaflets are presents on the higher order branches (e.g., *Moringa*); Each leaflet of a compound leaf is called a pinnule. The pinnules on one secondary vein are called pinna, e.g., *Albizia* (silk tree); pinnatifid when pinnately dissected to the central vein, but with the leaflets not entirely separate (e.g. *Polypodium*, *Sorbus*). In pinnately veined leaves, the central vein in known as the midrib. Leaf types constitute many important crude drugs of pharmaceutical importance.

6.5.2.3 Leaf Shape

The leaf shape, i.e., the shape of the leaf blade or lamina may vary (Fig. 6.23). It may be asymmetrical, when completely unsymmetrical (e.g., *Swietenia macrophylla*); acuminate, when leaf that tapers to a long point (e.g., *Ficus religiosa*, *Coffea arabica*, *Dioscorea*); mucronate, when leaf with an extended central vein, i.e., a leaf blade with an abrupt point at the apex (e.g., mulberry); emarginate, a leaf

having a notch at the apex or end (e.g., *Bauhinia*); ovoid: egg-shaped; obovate, when a leaf assumes the shape of a longitudinally halved egg, i.e., broader at the base and gradually tapering toward the apex (e.g., China rose and stramonium); cordiform, when the leaf is heart-shaped; oblong, when the leaf is long and equally broad all through its length (e.g., banana); spathulate, when the shape is like that of a spatula or spoon (e.g., Calendula); oval, when broad at the middle and narrow toward each end; lanceolate, when the leaf is broader in the middle and gradually tapers toward the two ends (e.g., Nerium, Polyalthia); acicular, when the leaf is long, narrow and cylindrical, i.e., needle-shaped (e.g., Pine), subulate, when narrow and tapering toward one end (e.g., onion); linear, when the leaf is long, narrow and flat (e.g., grasses); elliptical, when a leaf assumes the shape of an ellipse. In this case, the leaf is long and is almost equally expanded all through its length (e.g., guava, periwinkle); ovate, when the shape is inversely obovate (e.g., *Terminalia*); rotund or orbicular, when the blade is circular in outline with the petiole arising from the center (e.g., water lily); cordate, when the leaf acquires the shape of the heart (e.g., piper betle); obcordate, when it is inversely heart-shaped, the shape is called (e.g., oxalis); reniform, a kidney-shaped leaf (e.g., Indian pennywort); oblique, when the two halves of the blade are unequal and the leaf assumes a narrowly ovate shape (e.g., neem); sagitate, when the leaf is arrow—shaped (e.g., sagittaria, Coco-yam); hastate, when the two lobes of a sagitate leaf are directed outwards (ipomoea); cuneate, when the leaf is wedge-shaped (e.g., Pistia); falcate, a sickle-shaped leaf (e.g., Eucalyptus); lyrate, when the shape is like that of a lyre, i.e., with a large terminal lobe and some smaller lateral lobes (e.g., mustard, radish); pedate, when the leaf looks like the claw of a bird, with the lobes spreading outwards (e.g., Vitispedata). The shape of the leaf lamina varies from plant to plant (Fig. 6.23) and often provides useful diagnostic character for the identification of different leaf drugs.

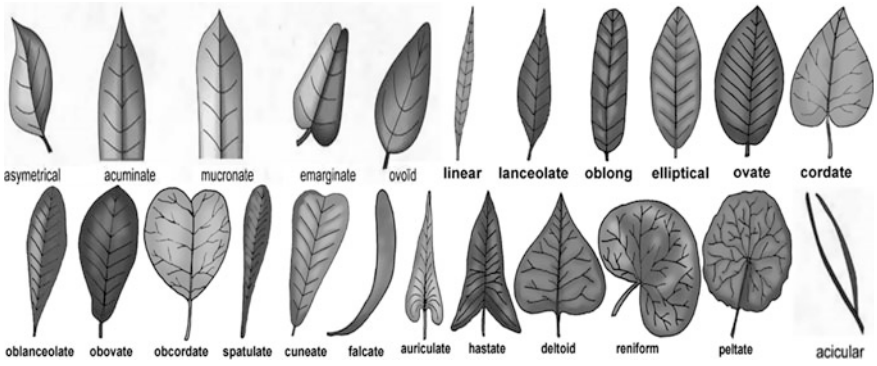


Fig. 6.23 Different types of leaf shape

6.5.2.4 Incision of the Lamina

In pinnately veined leaf (lamina with one prominent mid rib), incision may be pinnatified—when the incision of the margin is half—way or nearly half-way down toward the mid rib as in poppy; pinnatipartite—when the incision more than half the way down toward the mid rib as in radish, mustard, etc.; pinnatisect—when the incision is carried down to near the mid rib as in some ferns, *Quamoclit*, *Cosmos* etc. and pinnate compound—when the incision of the margin reaches the mid rib, thus dividing the lamina into a number of leaflets as in pea, gram, *Cassia*, etc. In palmately veined leaf (lamina with more than one prominent mid rib), incision may be palmatified, when the incision of the margin is half—way or nearly half-way down toward the leaf base, e.g., passion flower, cotton, etc.; palmatipartite—when the incision more than half the way down toward the leaf base, e.g., castor, papaw; palmatisect—when the incision is carried down to near the leaf base, e.g., *Manihot*, *Cannabis*, *Arisaema* and palmate compound—when the incision carried down to the base of the leaf blade as in *Bombax*, *Gynandropsis*.

6.5.2.5 Leaf Arrangement on the Stem: Phyllotaxy and Fibonacci Sequence

In plants, the arrangement of leaves, scales, and flowers around the stem is highly regular (Fig. 6.24). The pattern of arrangement of these lateral organs along the plant stem is called phyllotaxy or phyllotaxis, means 'leaf arrangement' in Greek. Phyllotaxis is important in positioning leaves so that they do not shade each other, and botanical phyllotaxis is based on some mathematical principles (e.g., Fibonacci numbers) that have been used in a number of sculptures and architectural designs. The basic phyllotactic patterns in the plant kingdom are opposite, whorled, or alternate and in some cases these patterns are species specific and ensure botanical identity.

In opposite phyllotaxis, a pair of leaves occur at each node. Opposite phyllotactic patterns may be further divided into (i) distichous or (ii) decussated phyllotaxis. In distichous phyllotaxis, the best-studied example is *Zea mays*, in which the successive leaf primordia are placed each at 180° from the previous one. Distichous phyllotaxis is characteristic of the grasses. *Pisum sativum* is a well studied example of a dicotyledonous plant with distichous phyllotaxis. In decussated phyllotaxis, two leaves are formed per node, arranged opposite at each node, but each successive pair of leaves is oriented perpendicular at right angles (90°) to the next pair at the next node. The divergence angle between successive leaf pairs is 90°. Decussate phyllotaxis is characteristic of the Lamiaceae (e.g., Coleus, Mentha and Salvia). Other examples of decussate genera are *Acer*, *Antirrhinum*, *Anagallis*, *Calotropis*, *Catharanthus*, *Hypericum*, *Ixora*, *Ocimum,* and *Psidium*. Interestingly, some decussate plants, such as *Salvia*, retain the decussate pattern throughout their entire life span, whereas others such as *Antirrhinum* undergo a transition to spiral phyllotaxis after induction of flowering. In some plants, subopposite

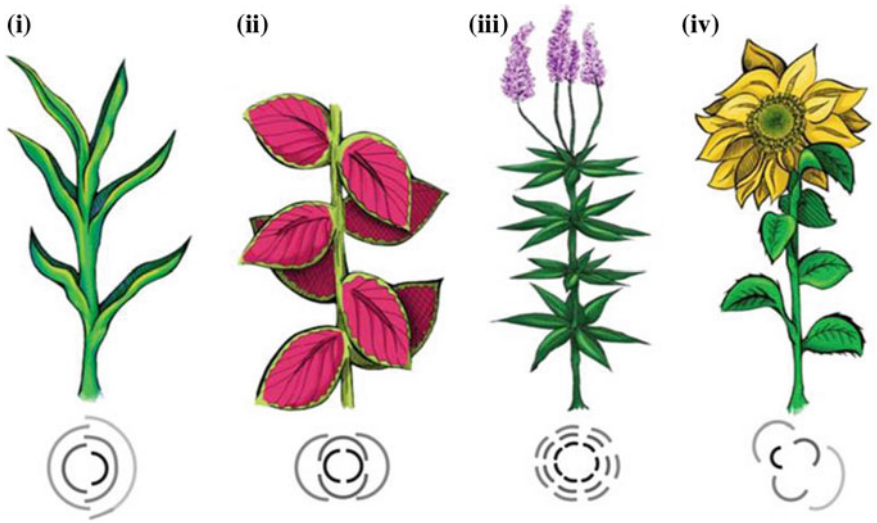


Fig. 6.24 Line diagrams of four major phyllotactic patterns showing relative leaf positions. (**i**) Opposite distichous with a divergence angle of 180º (*Z. mays*); (**ii**) opposite decussate with pairs of leaves at 90º (*Coleus* sp); (**iii**) whorled with three or more leaves originating from the same node (*Veronicastrum virginicum*); (**iv**) alternate (spiral) with a divergence angle of 137.58º (*Helianthus annus*)

(or pseudowhorls) phyllotaxis is observed where not all of the leaves are perfectly paired but the distance between the nodes is not far enough apart to be considered alternate in arrangement (e.g., *Wetria*).

Leaves may also be whorled if more than three leaves arise from the same level at the same node on a stem, e.g., *Allamanda*, *Alstonia*, *Nerium*, *Vangueria*. This arrangement is usually found on plants with particularly short internodes. The simplest case of whorled phyllotaxis is represented by tricussate (trimerous) phyllotaxis, in which three leaves are formed per node (e.g., *Nerium oleander).* These leaves are positioned symmetrically at 120° from each other, and the divergence angle between whorls of successive nodes is 60°. Up to ten leaves per node are formed by plants of the genus *Galium* (e.g., *G. verum).* As a general rule, the leaves in whorled systems are formed above the gaps between the leaves of the preceding whorl. Examples of trees with whorled phyllotaxis are *Brabejum stellatifolium* and the related *Macadamia* genus. Flowers commonly exhibit whorled phyllotaxis; the organs are frequently arranged in whorls of 3–5 units per node. The standard flower consists of four concentric whorls, the sepals, the petals, the stamens, and the carpels. Normally, the number of organs per whorl is strictly regulated, resulting, for example, in trimerous phyllotaxis in flowers of the Liliaceae, in quadrimerous phyllotaxis in the two outer whorls of crucifer flowers, such as *Arabidopsis*, and pentamerous phyllotaxis in the two outer whorls of flowers in Rosaceae and Solanaceae. In plants with a rosette of radical leaves or with whorls of leaves or in plants with crowded leaves (e.g., *Acalypha*, *Begonia*, garden

nasturtium, wood–sorrel, Indian pennywort) leaves are distributed forming a mosaic pattern with the smaller leaves fitting into the interspaces of the broader ones.

The spiral arrangement of leaves on the stem is called spiral phyllotaxis (Fig. 6.25). Spiral phyllotaxis is the most common arrangement of leaves in flowering plants and ferns. One leaf is formed per node, with the divergence angle between two successive leaves approaching the Fibonacci angle of 137.50°. The angle formed between a line drawn from the stem to the leaf and a corresponding line for the next leaf, generally a fixed angle, called the divergence angle. The divergence angle must be such as to minimize blockage of lower leaves by higher leaves. Many important plants, e.g., *Arabidopsis*, tomato, tobacco, lupin, sunflower, poplar, etc., exhibit spiral phyllotaxis. Many gymnosperms, e.g., *Araucaria*, *Pinus* and *Ginkgo* and ferns, e.g., *Dryopteris*, *Osmunda* also have spiral phyllotaxis.

As a stem grows, leaves tend to appear arranged around the stem in a way that optimizes yield of light. In essence, leaves form a helix pattern around the stem, either clockwise or counterclockwise, with (depending upon the species) the same angle of divergence. There is regularity in these angles and they follow the numbers in a Fibonacci sequence: 1/2, 2/3, 3/5, 5/8, 8/13, 13/21, 21/34, 34/55, 55/89. These ratios (1/2, 1/3, 2/5, 3/8, 5/13, 8/21…) are the angular spiral divergences of one leaf from another. Upon analyzing these figures, one realizes that each number of the numerator and each number of the denominator is the sum of the two preceding numbers (2 + 3 = 5, 3 + 5 = 8, 8 + 13 = 21, and so on).

Looking along the axes, leaves that are organized along a spiral and the angle formed between two successive leaves is more or less always the same. Phyllotaxy 1/2 or 2-ranked or alternate distichous, for instance, are separated by an angle of 1/2

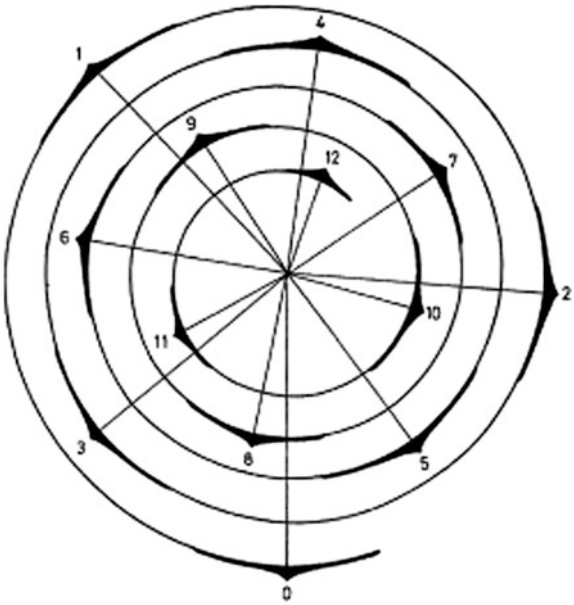


Fig. 6.25 The divergence angle formed between two successive leaves may be obtained from the figure. Image from http://tinyurl.com/32ny6wt

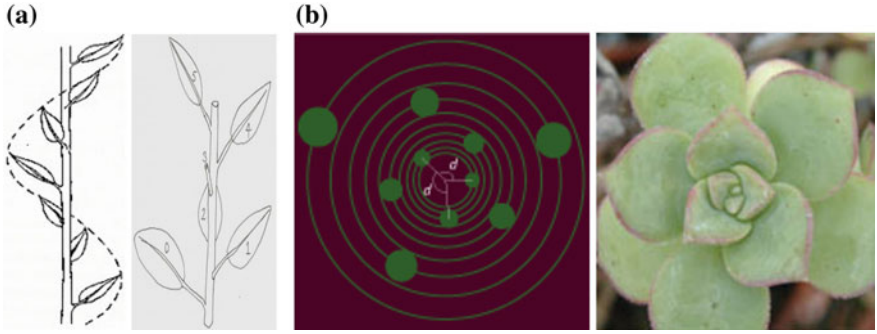


Fig. 6.26 **a** A repeating spiral can be represented by a fraction describing the angle of windings leaf per leaf. **b** In spiral phyllotaxis, botanical elements grow one by one, each at a constant divergence angle *d* from the previous one. This is the most common pattern, and most often the divergence angle *d* is close to the golden angle, which is about 137.50°. The latter case gives rise to fibonacci phyllotaxis

half or 180°, e.g., grasses, elephant grass (*Typha*), traveler's tree (*Ravenala*), ginger, *Vanda*, *Belamcanda*, *Iris*. In these cases, the third leaf stands over the first and the genetic spiral makes one complete revolution to come to that leaf, and it involves two leaves. The fourth leaf stands over the second, the fifth over the first and the third, and so on. Thus, there are only two orthostichies, i.e., leaves are arranged in two rows or ranks or distichous. A repeating spiral can be represented by a fraction describing the angle of windings leaf per leaf (Fig. 6.26).

In beech and hazel, the angle is 1/3 (120°)—three leaves in one circle; in oak and apricot, it is 2/5 (144°)—five leaves in two gyres; in sunflowers, poplar, and pear, it is 3/8 (135°)—eight leaves in three gyres; and in willow and almond, the angle is 5/13 (138°)—thirteen leaves in five gyres. This series tends to a limit close to $360° \times 34/89 = 137.52$ or 137° 30′, an angle known mathematically as the golden angle. In the series, the numerator indicates the number of complete turns or gyres until a leaf arrives at the initial position and the denominator indicates the number of leaves in between two points. The numerator (1 + 1 + 2 + 3 + 5…) and denominator (2 + 3 + 5 + 8 + 13…) normally consist of a Fibonacci number and its second successor in the Fibonacci series or numbers: 0, 1, 1, 2, 3, 5, 8, 13. The first two numbers in the Fibonacci series or sequence are 1 and 1, or 0 and 1, depending on the chosen starting point of the sequence, and each subsequent number is the sum of the previous two. Botany is a gold mine of spirals and Fibonacci numbers. The arrangement of seeds in the sunflower, the scaly plates in the pineapple, and the bracts in pinecones are other examples of Fibonacci numbers.

Spiral arrangements are most frequent, and they are classified by the number of spirals (parastichies) they exhibit. Parastichy is a hypothetical spiral line connecting the bases of a series of leaves on a stem they display. These spirals normally come in two families, yielding a pair of numbers, called parastichy numbers. If the parastichy numbers have no common divisor other than 1, the pattern is a spiral phyllotaxis. If the parastichy numbers do have a common divisor *k*, then the pattern

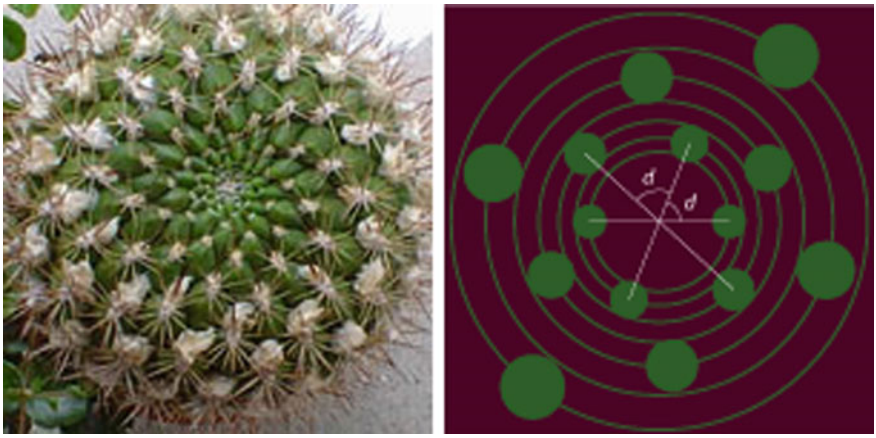


Fig. 6.27 In multijugate phyllotaxis, two or more botanical elements (two in the example *above*) grow at the same node. Elements in a whorl (group of elements at a node) are spread evenly around the stem, and each whorl is at a constant divergence angle *d* from the previous one. Often, multijugate patterns look very similar to spiral patterns, and the only way to detect them is to count the number of spirals visible in the pattern

is multijugate (more precisely *k*-jugate) and there are *k* elements at each node. The notion of parastichy numbers can be extended to distichous phyllotaxis with parastichy numbers (1, 1) and whorled with parastichy numbers (*k*, *k*) (Fig. 6.27).

Often, multijugate patterns look very similar to spiral patterns and the only way to detect them is to count the number of spirals visible in the pattern (called parastichies). If the parastichy numbers have no common divisor other than 1, the pattern is a spiral phyllotaxis. If the parastichy numbers do have a common divisor *k*, then the pattern is multijugate (more precisely *k*-jugate) and there are *k* elements at each node. Aonium has parastichy numbers (2, 3), since 1 is the only common divisor of 2 and 3, this is a spiral pattern. Since spiral phyllotaxis can be viewed as 1-jugate, the notation 1(2, 3) is also used for this pattern (Fig. 6.28).

Gymnocalycium has parastichy numbers (10, 16), which have the common divisor $k = 2$. Hence this is a multijugate pattern (more precisely 2-jugate). The notation 2(5, 8) is also used to classify this pattern. Parastichy numbers of shoot apical meristems of a gymnosperm *Norway spruce* are (8, 13), and that of an angiosperm *Artichoke* are (34, 55). Other examples of Spiral phyllotaxis include: aloe, cabbage, pine, sunflower. The white Lily has 3 petals, Ranunculus has 5 petals, Marigold has 13 petals, Aster has 21 petals and Daisies, and Sunflowers have 34, 55, or 89 petals depending on variety. Equally, depending on variety, Daisies and Sunflowers have floral primordia arranged in 34 clockwise spirals and 55 counterclock spirals—denominated parastichous spiral phyllotaxis (34, 55), some daisy and sunflower varieties have a (55, 89) phyllotaxis while others have a (89, 144) phyllotaxis. All these numbers of petals and seed spirals belong to the Fibonacci series.

Fig. 6.28 This Aonium has parastichy numbers (2, 3). Since 1 is the only common divisor of 2 and 3, this is a spiral pattern. Since spiral phyllotaxis can be viewed as 1-jugate, the notation 1(2, 3) is also used for this pattern

The number of visible spirals (parastichies) in spiral arrangements is most often Fibonacci numbers (1, 1, 2, 3, 5, 8, 13, 21…), and the angle between successive leaves is close to the Golden Angle—about 137.5°. This frequent type of pattern is called Fibonacci phyllotaxis. Fibonacci numbers and the Golden Angle have a precise mathematical relationship. With larger Fibonacci pairs, the pattern becomes complex and non-repeating. Most pineapples have 5, 8, 13, or 21 spirals of hexagons in increasing steepness on their rind surface. The petal count of field daisies, the seed head of sunflower, and pine cones exhibit Fibonacci spirals. This phyllotactic pattern creates an optical effect of cris-crossing spirals. In the botanical literature, these designs are described by the number of counterclockwise spirals

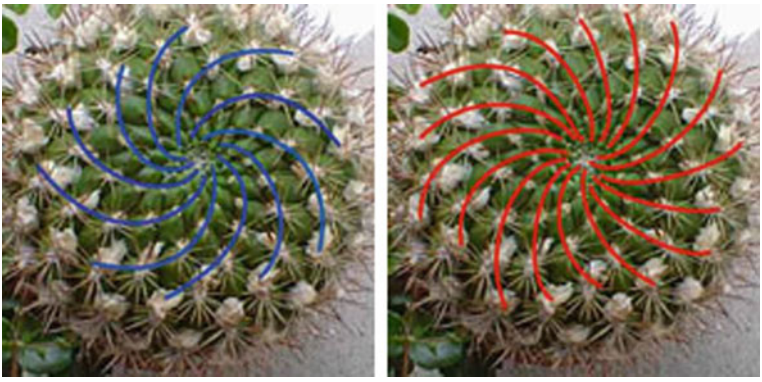


Fig. 6.29 This gymnocalycium has parastichy numbers (10, 16), which have the common divisor $k = 2$. Hence this is a multijugate pattern (more precisely 2-jugate). The notation 2(5, 8) is also used to classify this pattern

Fig. 6.30 Fibonacci numbers in pineapple skin hexagons. The skin of the pineapple fruit is made of hexagons, stuck together, and then wrapped to form a cylinder. Connecting hexagons in line, three different types of bands winding around the pineapple are evident as shown above *green bands*, *blue bands*, and *red bands*. It is well-known that pineapple exhibits consecutive Fibonacci numbers, such as 5-8-13 or 8-13-21

and the number of clockwise spirals (Figs. 6.29 and 6.30). Leonardo da Vinci was the first to suggest that the adaptive advantage of the Fibonacci pattern in plants is to maximize exposure to dew. Current thinking supports this interpretation; exposure to rainfall and sunlight are also maximized.

In alternate phyllotaxis, a single leaf is attached at each node. The leaves may be arranged in straight rows or spiral along the length of the twig. In an equiangular spiral, an equal portion of the circumference of the stem separates the successive leaves from each other. More than 80% of the 250,000 higher plant species have an alternate phyllotaxis, as in the case of China rose, potato, araucaria, yucca, sunflowers, and members of Rubiaceae (Fig. 6.31). In alternate distichous phyllotaxis, leaves or other botanical elements grow one by one, each at 180° from the previous one.

Fig. 6.31 A twig of China rose showing alternate phyllotaxis

The alternate arrangement of leaves in terms of ranking may be two-ranked, three-ranked, five-ranked, etc. In two-ranked, leaves alternate at 180° on the two sides of the twig, and in this system the third leaf is found directly over the first leaf and the fourth directly above the second. Two-ranked is described in the fraction 1/2. The numerator is the number of revolutions (1) around the twig and the denominator (2) means that two leaves were encountered in this one spiral of 360°. Examples are the grasses, sycamore, birch, elm, and linden. Three-ranked is described in the fraction 1/3, i.e., 3 leaves were encountered in this one spiral of 360°. Examples are the sedges, false hellebore, and sometimes beech. Five-ranked is described in the fraction 2/5; the figure 2/5 indicates that two circles around the twig encountered five leaves. This arrangement is the most common among the hardwoods as oaks, cherry trees, tulip trees, walnuts, hickories, sweet gum, and others. Eight-ranked is 3/8. Examples are holly, bayberry, and sweet fern. Thirteen-ranked is 5/13. Examples are willows and almond. These ratios (1/2, 1/3, 2/5, 3/8, 5/13, 8/21…) is the angular spiral divergence of one leaf from another. Upon analyzing these figures, one realizes that each number of the numerator and each number of the denominator is the sum of the two preceding numbers, i.e., 2 + 3 = 5, 3 + 5 = 8, 8 + 13 = 21 and so on. These are Fibonacci numbers. Leaf phyllotaxy and the Fibonacci numbers are naturally occurring mathematical phenomena: Botany seems to be a gold mine of spirals and Fibonacci numbers.

Alternate phyllotaxis can also be divided further into spiral or multijugate phyllotaxis. In spiral phyllotaxis, leaf primordia grow one per node, each at a constant divergence angle of 137.5° from the previous. In multijugate phyllotaxis, two or more leaf primordia grow at the same node. Leaf primordia of a node are spread evenly around the stem; each group of leaf primordia of a node is at a constant divergence angle of 137.5° from the leaf primordia group of the previous node.

Fibonacci sequence or numbers are: 0, 1, 1, 2, 3, 5, 8, 13, 21, 34, 55, 89, 144, 233, 377, 610… The sequence extends to infinity and contains many unique mathematical properties. After 0 and 1, each number is the sum of the two prior numbers. A Fibonacci number divided by the previous number approximates 1.618, which refers to the Golden Ratio or Golden Mean, also called Phi and the inverse of 1.618 is 0.618. These ratios can be found throughout nature, architecture, art and biology, the mathematical basis for the shape of the Parthenon, playing cards, sunflowers, pine cones, snail shells, breaking waves, the comet's tail, and the spiral galaxies of outer space.

Phyllotactic systems are remarkably stable, e.g., decussate plants maintain the initial pattern throughout vegetative growth, and sometimes during their entire life cycle (e.g., Lamiaceae). The phyllotactic patterns, however, can change, e.g., many decussate plants, such as snapdragon *Antirrhinum majus)* or *Epilobium* change to spiral phyllotaxis during the transition to flowering; *Helianthus microcephalus* and *H. tuberosus* remain decussate during the entire vegetative phase and only turn to spiral phyllotaxis at the onset off lowering, while *H. annuus* and other members establish spiral phyllotaxis after formation of a few leaf pairs. Therefore, decussate

and spiral phyllotaxis may in some cases share a common basis, and only the timing of transition may distinguish them.

6.5.3 Characteristics of the Petiole

Petiole or leafstalk attaches leaf blade to the stem while sessile leaf (leaf without petiole or apetiolate) attaches leaf blade directly to the stem. Subpetiolate leaves are nearly petiolate, or have an extremely short petiole, and appear sessile. In clasping leaves, the blade partially or wholly surrounds the stem, often giving the impression that the shoot grows through the leaf and under such condition, the leaf is called perfoliate, e.g., *Claytonia perfoliata*. In peltate leaves, the petiole attaches to the blade inside from the blade margin. In some plants, the petioles become flattened and widened, and the true leaves may become reduced or vanish altogether. These are known as phyllodes or phyllodia, or cladophylls. Thus, the phyllode comes to serve the purpose of the leaf. Phyllodes are common in the genus *Acacia*, especially the Australian species, at one time put in *Acacia* subgenus *Phyllodineae*. Sometimes, especially on younger plants, partially formed phyllodes bearing reduced leaves can be seen. In *Acacia koa*, the phyllodes are leathery and thick, allowing the tree to survive stressful environments. Petiole is pulvinate in Caesalpiniaceae. The petiole allows partially submerged hydrophytes to have leaves floating at different depths and helps to float the free floating hydrophytes like water hyacinth. There may or may not be normal pinnate leaves at the tip of the phyllode. In plants such as rhubarb (*Rheum rhabarbarum*), the petiole ('stalk') is harvested as a crop. The petiole grows directly from the root and produces the rhubarb leaf at its end. Botanically it is categorized as a vegetable and culinarily used as a fruit. Celery is a petiole, Chinese cabbages, cardoons, sweet fennel petiole, petioles of *Colocasia esculenta,* etc., are used as vegetables and many of them are rich in vitamin A, vitamin C, and calcium; sheath petiole of grasses and other monocot, spongy petioles of water hyacinth. Petiole character (e.g., anatomy) may be of special for taxonomic identification of different species of *Senna* as well as different members of the family Fabaceae, Lamiaceae, Lauraceae, and others.

A stipule is an appendage present at the base of the petiole of many dicotyledons. Stipules may be lasting and not be shed (a stipulate leaf, such as in roses and beans), or be shed as the leaf expands, leaving a stipule scar on the twig and the leaf without stipules are called exstipulate (e.g., mango and all monocots). The situation, arrangement, and structure of the stipules are called the stipulation, which may be (i) free-lateral (*Hibiscus*), (ii) adnate (Rose), (iii) intrapetiolar (Gardenia), (iv) interpetiolar (Ixora, Moringa), (v) ochreate (Polygonaceae), (vi) opposite (*Ficus elatica*), (vii) foliaceous (*Alchemilla mollis*, *Pisum sativum*), (viii) tendrillar (Smilax), (ix) spiny (*Acacia*, *Prosopis pallida* (e.g., *Zizyphus*), (x) glandular (*Euphorbia pteroneura*)

6.5.3.1 Leaf Margins

The leaf margin is the boundary area extending along the edge of the leaf. There are lots of different types of leaf margins that are important for plant identification and provide important diagnostic character for the identification of a leaf drug (Fig. 6.32). The followings are some common types.

Entire marginis smooth all the way around, neither toothed, serrated, lobed, or compound, i.e., simple with smooth margins (*Artocarpus heterophyllus*, *Premna serratifolia*); in repand or sinuous—margin entire and slightly undulate or wavy or slightly wavy line along the edge of a leaf (*Ficus religiosa*, *Mangifera indica*), in crenate margin leaf (asam lata, *Bryophyllum*, *Centella*), the edge has blunt, rounded teeth; sinuous or sinuate margin describes the sinuous, slightly wavy line along the edge of a leaf; in sinuate—extremely wavy or undulated margin (*Polyalthia longifolia*); serrate: having a sharp edge, 'saw-like' teeth and the teeth directed upward (China rose, rose, *Azadirachta indica*); serrated margin with small white teeth pointed toward leaf tip (*Aloe vera*); doubly-serrated, the 'saw-like' teeth have even smaller teeth; serrulate margin is similar to serrate, but has smaller, evenly spaced teeth; dentate—leaf margin has triangular, tooth-like edges, directed outward at right angles to the margin of the leaf (melon, water lily); incised margin leaf has deep, irregular teeth; lobate: lobed; lobed margin has deep, rounded edges; scalloped: with a scalloped margin; palmate: like the fingers of a hand spread open; digitate: finger like; bipinnatisect: with 2 levels of petioles which segments are sessile; tripinnatisect: with 3 levels of petioles which segments are sessile; pinnatisect: with similar parts on each side of the central axis and sessile; palmatisect: with palmate veins and lobes split to the base of the blade; pedate: palmately divided which lateral segments also divided; palmatilobate: palmate leaf with rounded lobes; bipartite: divided into two parts. tripartite: divided into three parts; palmatipartite: divided almost to the leaf margin. pinnatifid: with pinnated divisions. In addition to these types, the leaf margin may vary greatly under various

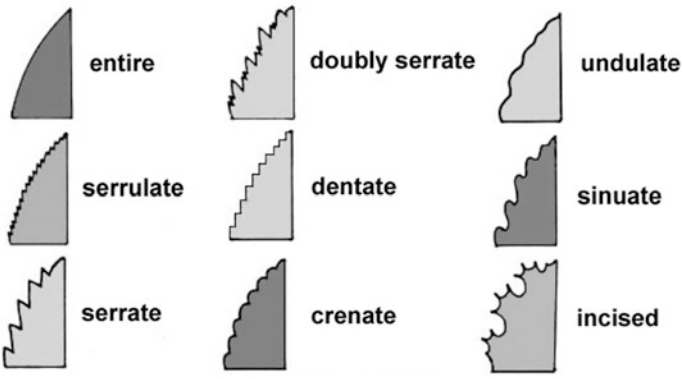


Fig. 6.32 Different types of leaf margins

conditions of growth. Bachu leaf margin is dentate in the upper two-thirds of the leaf and serrate toward the base.

6.5.3.2 Leaf Apex

An apex or tip of different leaves vary greatly from plant to plant (Fig. 6.33). Apex of the leaf may be acuminate, acute, obtuse, caudate, or acuminate, when it is drawn out into a long slender tail (*Ficus religiosa*) cuspidate, retuse; emerginate, mucronate, cirrhose, etc. Acuminate—tip prolonged into a narrow point; acute—tip tapering to a sharp point in the form of an acute angle (China rose); obtuse almost rounded tip (*Ficus bengalensis*); cuspidate—tip with a hard, spiny point (date palm, screw pine, pine apple); retuse—tip slightly indented; emerginate—tip deeply indented or notched; mucronate—abruptly tipped with a short point and cirrhose-tip ending in a tendril or in a slender, curled appendage; truncate, when it ends abruptly, as if cut off in a straight line as in Indian sago palm (*Caryota urens*); retuse, when the obtuse or truncate apex is furnished with a shallow notch as in water lettuce (*Pistia*); emerginate, when the apex is provided with deep notch as in *Bauhinia*, mucronate, when the rounded apex abruptly ends in a short point (*Ixora*); cirrhose (cirrus—a tendril or a curl), when it ends in a tendril (glory lily), or a slender, curled, thread—like appendages (banana). Apices of leaf greatly vary from plant to plant and are useful in classification and identification.

6.5.3.3 Leaf Bases

The base of a leaf is the lower part of the lamina, where it is attached to the petiole or stem. Leaf base is cuneate, if it is sharp-pointed with an angle less than 45° between opposite sides; acute, if it is sharp-pointed with an angle between 45° and 90° at the position where the lamina joins the petiole; obtuse, if it is blunt or narrowly rounded with opposite sides forming an angle greater than 90° at the

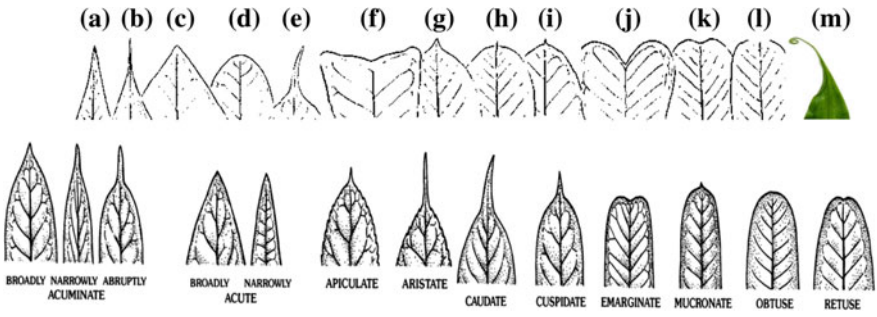


Fig. 6.33 Leaf apex: **a** acuminate, **b** aristate, **c** acute, **d** obtuse, **e** caudate, **f** emerginate, **g** cuspidate, **h** mucronate, **i** apiculate, **j** obcordate, **k** retuse, **l** truncate, **m** cirrhose

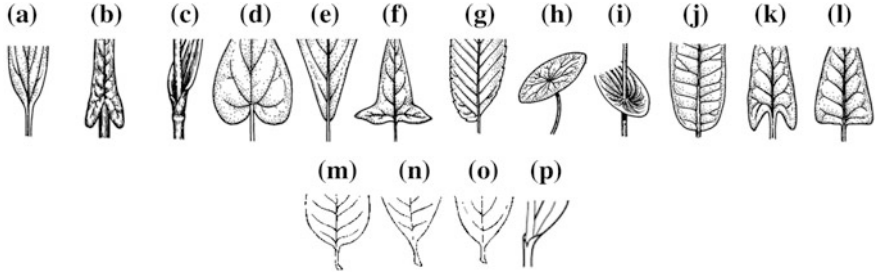


Fig. 6.34 Leaf bases: **a** attenuate, **b** auriculate, **c** clasping, **d** cordate, **e** cuneate, **f** hastate, **g** oblique, **h** peltate, **i** perfoliate, **j** round, **k** sagittate, **l** truncate, **m** rounded, **n** acute, **o** equilateral, **p** sheathing

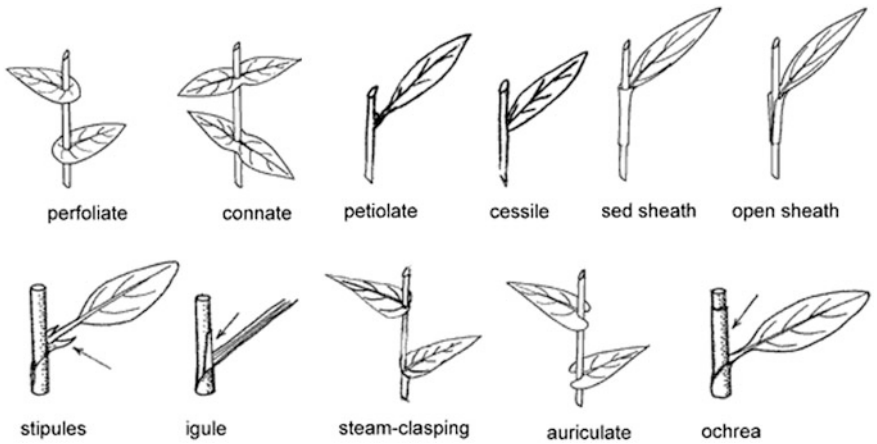


Fig. 6.35 Types of leal attachment to stem by bases

position where the lamina joins the petiole; rounded, if it is curved to form a full, sweeping arc; truncate, if it forms a flat-topped or squared-off shape; cordate base is heart or valentine-shaped; inequilateral base has asymmetrical left and right sides of different sizes or shapes; auriculate base has earlike lobes where the lamina joins the petiole, sheathing leaf base surrounding the stem (Fig. 6.34).

6.5.3.4 Leaf Attachment

Attachment of leaf base by sheath to plant stem may characteristically vary in different plant and that may be helpful for the identification of crude leafy drugs. The following types of leaf attachments are known (Fig. 6.35).

6.5.3.5 Leaf Surface

Surfaces of leaves provide many characteristics that are used in identification. Surfaces of a leaf may be smooth or may have some epidermal outgrowths. A surface is glabrous, if it is smooth or free from hairs; pubescent, if it is hairy; glaucous, if covered with a whitish powder or waxy coating; scabrous, if rough or harsh to the touch; puberulent if covered with very fine, down like hairs; villous, if covered with long, soft, shaggy hairs; tomentose, when it is densely covered with short, soft hairs; hirsute, if the hairs are short, erect, and stiff; and hispid, if they are dense, bristly, and harshly stiff; rugose, if wrinkled like leaves of the mint family (Lamiaceae); farinose, if covered with a meal-like powder or minute particles; scurfy, if covered with small scalelike particles; viscid (viscous), if covered with sticky or resinous secretion; glutinous—about the same as viscid; punctuate, if dotted with minute pits or translucent dots; papillate (papillose). If bears minute, pimple-like protuberances; tuberculate, if bears tubercles or warty protuberances; verrucose—about the same as tuberculate. Bachu surface is punctuated, dotted with projections formed by subjacent of scattered oil glands.

6.5.3.6 Leaf Persistency

Leaves may be fugacious, falling nearly as soon as formed; deciduous, falling at the end of the growing season; marcescent, withering at the end of the growing season but not falling until toward spring; or persistent, remaining on the stem for more than one season, the plant thus being evergreen.

6.5.3.7 Leaf Texture

Texture or feel of the leaf to the touch varies from leaf to leaf and is sometimes very important in its identification. The texture may be hyaline if it is thin and almost wholly transparent; chartaceous if papery, thin, pliable, and opaque but thin; scarious if thin and dry, appearing shriveled; and coriaceous or leathery if tough, thickish, and leathery and leather like and succulent if the leaf is fleshy, thick, soft, and juicy. Texture of Bachu leaf is rigid and coriaceous (thick and leathery) when dry but cartilaginous when moist.

6.5.3.8 Leaf Venation

The arrangement of the veins and veinlets and their mode of distribution in the leaf blade are called the venation. The veins consist of vascular tissues (xylem and phloem) of the leaf and are located in the spongy layer of the mesophyll. The veins connect the blade to the petiole and lead from the petiole to the stem. Venation is characteristic of the type of a leaf. The xylem typically lies on the adaxial side of the

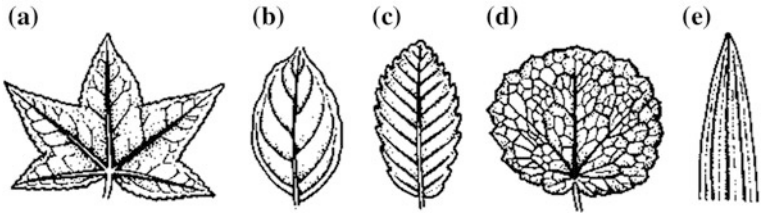


Fig. 6.36 Leaf venation—**a** palmate, **b** acruate, **c** pinnate, **d** reticulate, **e** parallel

vascular bundle and the phloem typically lies on the abaxial side. Leaf venation is basically of three types, e.g., reticulated, parallel, or dichotomous. (i) In reticulated venation, the veins are arranged in a net-like pattern, in that they are all interconnected like the strands of a net. Reticulated venation is the most common venation pattern and occurs in the leaves of nearly all dicotyledons such as Maple, Oak, and Rose except *Calophyllum* (parallel pinnate) and some other dicotyledons. (ii) In Parallel venation, the veins run parallel or nearly parallel to each other and are connected by smaller veins. Parallel venation occurs in the leaves of nearly all monocotyledons such as lilies, banana, rice, and other grasses, but *Dioscorea*, *Smilax,* and some aroids show reticulate venation. (iii) In dichotomous venation, the veins branch off from one another like the branches of a tree. This is the rarest venation pattern and occurs in the leaves of some ferns and in the gymnosperm, e.g., *Ginkgo biloba*. Reticulate venation may be pinnate (unicostate), arcuate, palmate (multicostate), etc., while parallel venation may be pinnate (unicostate), convergent, divergent, etc. (Fig. 6.36).

Reticulate venation may be pinnate (unicostate—one strong mid rib), e.g., *Ficus*, *Mangifera*, *Psidium* etc. or palmate (multicostate—many strong veins), e.g., *Carica*, *Lagenaria*, *Racinus*, *Hibiscus* are examples of palmate divergent venation while *Ziziphus*, *Cinnamomum* stand for palmate convergent venation. Parallel pinnate (unicostate—one strong mid rib) venation is found in *Musea*, *Zingiber*, *Canna*, *Curcuma,* etc., and parallel palmate (multicostate—many strong veins)

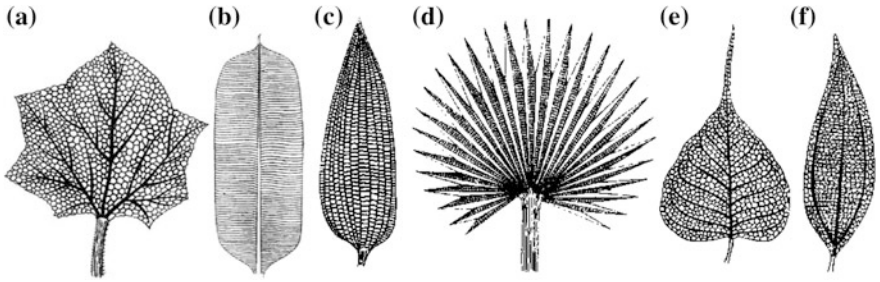


Fig. 6.37 Leaf venation **a** multicostate (pinnate) divergent, **b** parallel pinnate (unicostate), **c** parallel palmate (convergent) **d** parallel palmate (divergent), **e** reticulate unicostate (pinnate), **f** multicostate (palmate) convergent

convergent venation is present in the leaf of Ichornia, Bambusa, Oyza, Triticum, and in other grasses while parallel palmate (multicostate—many strong veins) divergent venation is present in the leaf of palmira palm (Fig. 6.37).

Parallel venation (in monocotyledons) and reticulate venation (in dicotyledons) are the broadly divided two types. The venation patterns are being determined in terms of veinlets (vein-islets) and veinlet termination numbers located per square millimeter of the leaf surface midway between the midrib and the margin. A vein termination is the ultimate free termination of veinlet. It has been shown that the number of veinlets/vein-islets per unit area of leaf surface is constant for any given species of plant and can be used as a character for the identification of species (Wallis 2005). Identification of leaf drugs using venation is considered as one of the most reliable and convenient means for distinguishing them from allied species or superficially resembling plant species, especially in the absence of reproductive parts. Like human fingerprints, veination patterns of drug plants can be used as a scientific tool to authenticate drugs in their crude form and for that Venation Image Database System (VIDS) may be designed.

6.5.3.9 Leaf Anatomy

Leaves of monocot and dicot plants like stem and root also comprise the three tissue systems—ground, dermal, and vascular (Fig. 6.38). The dermal tissue system contains a lower epidermis and an upper epidermis. The cuticle on the upper epidermis is thicker than that of lower epidermis in dorsiventral dicot leaf and undifferentiable in isobilateral monocot leaf. Stomata are present in both the epidermis of monocot leaf but more often in the lower epidermis of dicot leaf except in some special cases. The cuticle helps to check transpiration and stomata are used for transpiration and gas exchange. In grass family of monocot, a few cells in the upper epidermis are enlarged to form motor cells called bulliform cells, which help in rolling and unrolling and thereby regulate moisture loss under water stress. The ground tissue system which takes place among the epidermal layers of leaf is termed as mesophyll tissue. It is undifferentiated in case of monocot leaf but most often is distinguished into spongy parenchyma on the abaxial that lower side and palisade parenchyma on the adaxial that is upper side in dicot leaf. Palisade parenchymas are vertically elongated cylindrical cells in one or more layers without intercellular spaces contain more chloroplasts than the spongy parenchyma cells. The function of palisade parenchyma is photosynthesis. Below palisade parenchyma toward lower epidermis, spherical, oval or irregularly shaped, loosely arranged chlorenchyma cells with numerous airspaces form spongy parenchyma. The mesophyll tissue, particularly spongy parenchyma cells encloses lots of airspaces. The existence of airspaces is a unique characteristic of spongy cells. Spongy cells facilitate the exchange of gases among the internal photosynthetic tissue (mesophyll) and the external atmosphere by the stomata with the help of airspaces. The airspace that is found next to the stoma is called respiratory cavity or substomatal cavity. The vascular tissue system is created of vascular bundles.

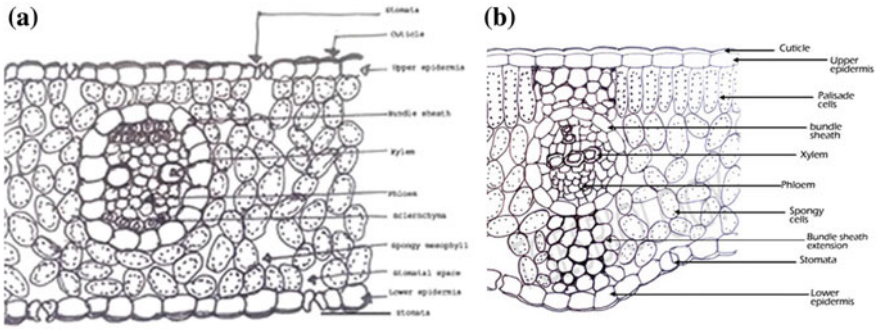


Fig. 6.38 Anatomical structures of **a** isobilateral (monocot, e.g., maize) leaf and **b** dorsiventral (dicot, e.g., sunflower) leaf

Vascular bundles are conjoint and collateral and composed of xylem and phloem. Xylem is present toward the upper epidermis, while the phloem toward the lower epidermis. Vascular bundles are surrounded by a compact layer of parenchymatous cells called bundle sheath or border parenchyma. Xylem consists of vessels and xylem parenchyma. Tracheids and xylem fibers are absent. In case of monocot leaf, the bundle sheath of the midrib vein is connected to the upper and lower epidermal layers by sclerenchyma cells representing bundle sheath extensions or hypodermal sclerenchyma. Protoxylem vessels are present toward the upper epidermis, i.e., exarch but endarch xylem is in monocot leaf. Phloem consists of sieve tubes, companion cells, and phloem parenchyma. Phloem fibers are absent. The vascular tissue creates the skeleton of the leaf, and they are termed as veins. The veins supply minerals and water to the photosynthetic tissue. So the morphological and anatomical features of the leaf assist in the physiological functions of it.

6.5.3.10 Modification of Leaf Structure

Epidermis

The epidermis of leaf generally consists of a single layer of compact cells with occasional stomatal openings, but becomes multilayered in some special cases like the leaves of *Piper betle* or *Ficus elastica*. The epidermal cells are tabular and show a complete absence of intercellular spaces except the stomatal pores. They appear flattened and square or rectangular in surface view or in transverse sections. The outer walls are often convex and thickened. The anticlinal and perichnal walls of the epidermal cells and thickenings on them vary from plant to plant. For example, straight-walled cells are present in *Senna* and Coca leaves; wavy-walled cells in *Stramonium*, *Belladonna,* and *Hyoscyamus*; beaded walls in *Digitalis lutea* and *Lobelia inflata*. The epidermal tissue includes several differentiated cell types including epidermal cells, guard cells, subsidiary cells, and epidermal hairs (trichomes). Cuticle covers the epidermal cells as an external protective layer.

The Cuticle

A plant cuticle is a non-cellular waterproof transparent protective film covering the epidermis of leaves and also present in young shoots and other aerial plant organs without periderm. Cuticles protect plants against desiccation, UV radiation and various kinds of physical, chemical, and (micro) biological agents. It consists of lipid and hydrocarbon polymers impregnated with wax. It is synthesized exclusively by the epidermal cells, usually very thin, but with excess deposition of pro-cutin it may produce ridges and become somewhat striated. Thick cuticle occurs in *Aloe* leaf and striated cuticles in *Belladonna*, *Digitalis,* and *Pilocarpus* sp.

Stomata

The leaf epidermis is covered with pores called stomata (sing. stoma). A stoma complex is consisted of a pore surrounded on each side by chloroplast-containing guard cells, and two to four subsidiary cells that lack chloroplasts (Fig. 6.39). The stoma complex regulates the exchange of gases and water vapor between the outside air and the interior of the leaf. Typically, the stomata are more numerous over the abaxial than adaxial epidermis of the leaf. Stomata are entirely confined to the lower epidermis in *Ficus*, *Buchu*, *Coca,* and Jaborandi leaves. In floating leaves of lotus, water lily, etc., where most or all stomata are on the upper or adaxial surface. In vertical or isobilateral leaves, such as those of many grasses, often have roughly equal numbers of stomata on both surfaces. Stomata are important epidermal structures of great taxonomic importance. Stomatal types, occurrence, their distribution, number of stomata per square mm of epidermis (stomatal number), and their ratio between the upper and lower epidermis sometimes offer important diagnostic characters for the identification of many leaf drugs.

Gourd Cells Five types of stomata recognized on the basis of form, and arrangement of the subsidiary cells is also important for diagnosis., e.g., (i) anomocytic or ranunculaceous (irregular-celled) type, found in *Digitalis purpurea*; (ii) anisocytic or cruciferous (unequal-celled) type, where the stoma remains surrounded by 3 or 4 subsidiary cells, found in *Stramonium*, *Belladonna,* and

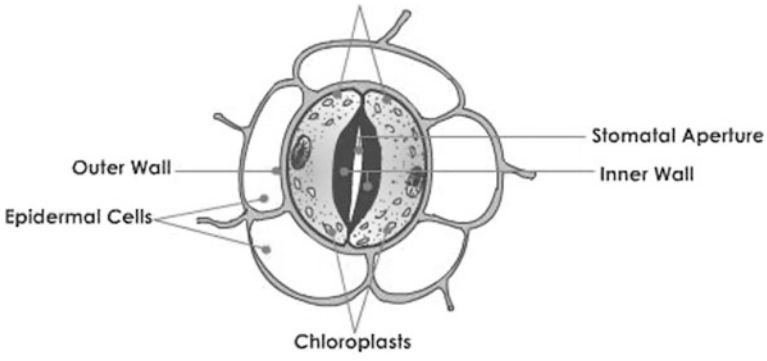


Fig. 6.39 Epidermal cells and stoma

Hyoscyamus leaves; (iii) paracytic or rubiaceous (parallel-celled) type, found in *Senna* leaves; (iv) diacytic or caryophyllaceous (cross-celled) type, found in many plants of Lamiaceae family, e.g., *Peppermint*, *Spearmint,* and *Thyme*; (v) actinocytic (radiate-celled) type, not very common in drug plants.

Cell Inclusions Cystoliths of calcium carbonate occur in the epidermal cells of the members of Cannabinaceae and Urticaceae; sphaerocrystals of diosmin in *Buchu* epidermis and mucilage is present in the epidermis of *Senna* and *Buchu* leaves.

Papillae Epidermal cells of some plants sometimes extend outward as dome-shaped or conical projections which are termed as papillae, the epidermis being called papillose. Papillae occur most frequently on the under surface of the leaves of *Coca* and *Cassia obovata*.

Trichomes Trichomes or epidermal hairs are elongated tubular outgrowths on the epidermal cells of most leaves, many herbaceous stem, flower, fruit, and seed. The occurrence and forms of the trichomes are very valuable characters for the identification of leaf drugs and detection of adulterants in them. Three types of trichomes are generally recognized; (i) covering or clothing trichomes, (ii) glandular trichomes, and iii. hydathodes and other special types. Any one type or more than one type of trichomes may occur on the same plant.

Covering or clothing trichomes may be unicellular or multicellular. The unicellular trichomes vary greatly, e.g., short, conical trichomes occur in Tea and Buchu (*Agathosma* sp.) levels; short, conical, and warty trichomes in *Senna*; large, conical, and longitudinally striated trichomes in *Lobelia*; long, thick-walled trichomes in Ailanthus, and T-shaped trichomes in *Artemisia absinthium*. They may also occur in a group as in *Hamamelis* leaf. The multicellular may be uni-, bi-, or multiseriate or even branched. The number of cells in the multicellular trichomes may vary from two to many cells. Uniseriate, 2 to 3-celled long covering trichomes are found in *Datura* and *Hyoscyamus*; 3 to 4-celled long in *Digitalis*, and 4 to 5-celled long in *Belladonna*. Biseriate multicellular trichomes occur on leaves of *Calendula officincilis*. Multiseriate trichomes are found in *Euphorbia hirta*. Branched multicellular trichomes may be stellate as in *Hamamelis* leaves or may be slender and elongated as in *Verbascum thapsus*. Covering trichomes function as protective agents, light screen for reducing rate of transpiration, climbing means, water-storing agents and also as seed dispersal agents.

Glandular trichomes usually have uni- or multicellular stalks and uni- or multicellular heads. The stalk may be uni- or multiseriate and short or long. The glandular trichomes may also be sessile being embedded in the epidermal cells. The type of the glandular trichomes may be characteristic of a plant family or genus, e.g., glandular trichomes with short unicellular stalks and multicellular rounded or oval heads are found in the Solanaceae and sessile glandular trichomes with multicellular heads, in which the individual cells radiate, are characteristic of the mint family Lamiaceae—a large family of aromatic herbs and shrubs. However, most glandular trichomes are multicellular, the simplest type having a uniseriate stalk with a single spherical glandular cell at the apex. This type of trichomes may he

found in *Digitalis* and *Belladonna* leaves. But most glandular trichomes of *Digitalis purpurea* have a unicellular stalk and a bicellular head. The glandular trichomes of the plants of the Asteraceae family have short biseriate stalks and bicellular glands. Trichomes having a multiseriate cylindrical stalk and a capitate rosette of secreting cells are found in Cannabis. Functions of the glandular trichomes include secretion and accumulation of poisonous substances, volatile oils, resins, mucilage, etc.

Hydathodes are special structures formed by the modification of some epidermal cells. Some of them resemble the stomata in structure but do not contain chloroplasts, and others resemble the glandular trichomes which are found on the leaves of *Piper betle*. Their main function is absorption or secretion of water.

6.5.3.11 Leaf as a Source of Drug Principles

Aloes are obtained from several sources, e.g., Barbados aloes from *Aloe barbadensis* of the West Indies, Socotrine aloes from *Aloe perryi* of East Africa and Cape aloes from *A. ferox* of South Africa. Aloes contain several glucosides. Belladonna is obtained from the dried leaves, tops, and to some degree the roots of *Atropa belladonna.* Leaves contain several alkaloids including hyoscyamine and atropine. Cocaine, a crystalline tropane alkaloid, is obtained from the leaves of the coca shrub, *Erythroxylon coca*, and related species contain cocaine. Buchu is derived from the dried leaves of the shrubs *Barosma betulina*, *B. serratifolia,* and *B. crenulata*. The active ingredients include mucilage, volatile oil, and polysaccharides. Digitalis is obtained from the dried leaves of Foxglove, *Digitalis purpurea*. It contains cardiac glycosides digoxin and digitoxin. Eucalyptus is the mature leaves of *Eucalyptus globulus* and contains an essential oil eucalyptol that is used in medicine. Hamamelis or Witch hazel is obtained from the dried leaves of *Hamamelis virginiana*. In some places, the bark, twigs, and sometimes the entire plant are utilized. The active principle is tannin. Henbane, *Hyoscyamus niger*, is a coarse smelly herb native to Europe and Asia. The leaves and flower tops contain several poisonous alkaloids: hyoscyamine and scopolamine. *Lobelia inflata*, the Indian tobacco, is the source of this drug that is secured from the dried leaves and tops of wild or cultivated plants. The piperidine alkaloid lobeline is the main ingredient. Pennyroyal, *Hedeoma pulegioides*, is a small aromatic annual found in poor soil in the eastern United States. The essential oil of pennyroyal is obtained by steam distillation from leaves and flowering tops. The dried leaves and tops of the plant contain essential oil consists chiefly of pulegone but also contains menthone, isomenthone, l-pinene, l-limonene, dipentene, menthol. Other chemical constituents include bitter principle and tannin. Senna is an ancient drug that is obtained from dried leaflets and pods of several species of *Cassia.* Alexandrian senna is from *Cassia acutifolia* and East Indian senna is from *C. angustifolia.* Senna leaf contains dianthrone glycosides (sennosides), and small amounts of anthraquinones including aloe-emodin and rhein 8-glucoside, mucilage; tannins, and flavonoids. Senna glycosides or sennosides are used in modern medicine as laxatives. Stramonium is derived from thorn apple or Jimson weed (*Datura*

stramonium). The active principles are alkaloids that include hyoscyamine, atropine, and scopolamine. Dried leaves and tops of *Artemisia absinthium* are the source of an essential oil characterized by the presence of *cis*-epoxyocimene, chrysanthenol and chrysanthenyl acetate.

Buchu consists of the dried leaves of *Barosrna betulma* (Thumb.) Bartle & Wendi; and other species of the family Rutaceae. The plants are small shrubs with opposite leaves.

6.5.4 Flower

In pharmacognosy, the term flower drugs is used in a collective sense for commercial purposes and the sample includes both flowers and inflorescences. In some cases, the sample may not contain a whole flower or inflorescence but only a part of the flower. However, for the sake of identification and detection of adulterants, pharmacy students should be familiar with the botanical description of a flower. Drugs obtained from flower/flowering parts include Clove, Pyrethrum, Saffron, Santonica, Chamomile.

The flower is a modified shoot of limited growth; bearing reproductive organs in a compactly arranged structure. There are about 250,000 known species of flowering plants. A typical flower consists of four floral parts, e.g., calyx, corolla, androecium (male), and gynoecium or pistil (female). All these four parts are composed of a number of individual units. The units of the calyx, corolla, androecium, and gynoecium are called sepals, petals, stamens, and carpels, respectively. Each stamen is differentiated into a filament (the stalk) and an anther (the pollen bearing sac), and the pistil is differentiated into an ovary (the lower swollen part containing the ovules), a style (the elongated tube), and a stigma (the expanded or modified tip of the style). All the four parts develop in an ascending order on the swollen end (the thalamus or receptacle or torus) of the floral axis or stalk, the pedicel (Fig. 6.40). Much of the variation among flowers is based on variation of these basic parts. Different forms, sizes, shapes, and colors of flowers play vital role to attract pollinators to effect pollination.

A flower that has all four whorls of floral parts is said to be a complete flower (e.g., hibiscus, lily) while lacking any one or more of these parts is incomplete flower (e.g., elms, willows, oaks, plantains). Unisexual flowers bear either male (♂) or female (♀) sex organ, and they are said to be staminate or pistillate flowers while a bisexual flower bears both male (stamen) and female (pistil) sex organs. When staminate and pistillate flowers occur on the same individual, the plant is called monoecious (e.g., corn, cucumber) whereas dioecious plants carry either male or female flowers on two separate plants (e.g., *Asparagus*, *Carica papaya*).

A flower has a superior or hypogynous ovary when the base of the ovary is located above where the sepals, petals, and stamens are attached and such flower is said to be superior (e.g., pelargonium, silene). The point of attachment of sepals, petals, and stamens is referred to as the receptacle or hypanthium, the fused bases of

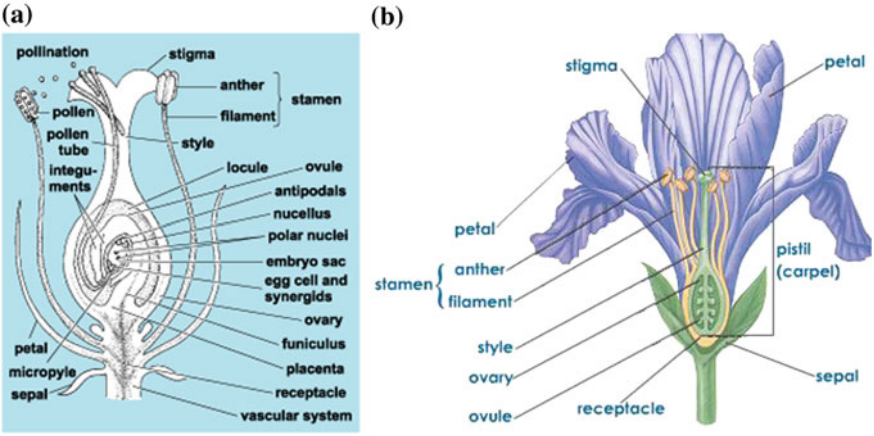


Fig. 6.40 **a** Labeled diagram of a generalized flower and **b** an example of China rose (*Hibiscus rosa sinensis* L.)

the three floral parts (e.g., tulips, *Hypericum perforatum*). An inferior flower has an epigynous ovary in which the sepals, petals, and stamens appear to be attached to the upper part of the ovary (e.g., cucurbits, daffodils, and sabatia). Some flowers show an intermediate type, where the receptacle partly surrounds the ovary; the petals and stamens branch from the receptacle about half-way up the ovary (e.g., cherry, peach, and almond). Flowers types in which the hypanthium forms a cuplike or tubular structure that partly surrounds the ovary are called perigynous. In such flowers, the sepals, petals, and stamens are attached to the rim of the hypanthium, and the ovaries of such flowers are superior (e.g., apple).

The parts of a flower may be free or united. Fusion of like parts (such as petals united to petals) is called connation. Fusion of unlike parts (stamens united to petals) is called adnation, and the contrasting condition is called free (stamens are free from petals). When like parts are not fused, they are said to be distinct (one petal is distinct from another petal). Fused structures may be united from the moment of origin onward, or they may initially be separate and grow together as one later in development.

In many different flowers, the petals of similar shape radiate from the center of the flower and are equidistant from one another. Such types of flowers are said to have regular or radial symmetry (actinomorphic flowers, e.g., stonecrop, morning glory). In these cases, any line drawn through the center of the flower will divide it into two similar halves. Flowers with irregular or bilateral symmetry have parts arranged in such a way that only one line can divide the flower into equal halves (zygomorphic flowers, e.g., mint, pea, and snapdragon). A few flowers have no plane of symmetry and are referred to as asymmetrical.

6.5.4.1 Inflorescence

A flower is said to be solitary, when a single flower is borne on caulescent or acaulescent stem. On the other hand, an inflorescence may be defined as a cluster of flowers arising from the main stem axis or peduncle. Inflorescences with youngest flower at the end of the main axis (rachis) are called indeterminate or racemose and with oldest flower at the end of the main axis are called determinate or cymose inflorescences. Following types of inflorescence are known (Fig. 6.41).

Raceme, inflorescence composed of a main axis and laterally borne flowers with pedicels of equal; cyme, the oldest flower terminates the main axis, scorpioid cymes have one-sides branching, forming a coiled inflorescence typical of the families Boraginaceae and Hydrophyllaceae; uniparous cyme, inflorescence whose main axis ends in a flower under which a single lateral twig develops; the process is repeated under each terminal flower; umbel, inflorescence composed of a main axis and laterally borne flowers with pedicels of equal length, all originating from the same point, typical of the familie Apiaceae; capitulum, inflorescence composed of flowers with no pedicel, all embedded in a flat receptacle, typical of the familie Asteraceae; spike, unbranched, indeterminate, elongated inflorescence composed of a main axis and laterally borne sessile flowers, i.e., with no pedicel length; biparous cyme, inflorescence whose main axis ends in a flower under which two lateral twigs develop; the process is repeated under each terminal flower; corymb, inflorescence composed of a main axis and laterally borne flowers with pedicels of unequal length, all ending at the same height; spadix, thick, fleshy spike inflorescence composed of unisexual apetalous flowers (male above, female below) with no pedicel, often surrounded by a vase-shaped or funnel-like modified leaf or spathe which is often brightly colored, characteristic of the arum family (Araceae).

Hypanthodium, an inflorescence with flowers on wall of a concave capitulum, as in *Ficus*; verticillaster, whorled dichasia at the nodes of an elongate rachis; panicle, a branched or compound raceme (i.e., main rachis with branches bearing flowers on pedicels); spikelet or locusta, a small spike; the basic inflorescence unit in grasses and sedges; catkin or ament, a spike-like inflorescence of unisexual (male catkin-*Morus alba*, demale catkin-*Morus nigra*), apetalous flowers, often pendent and falling as a unit. They are found in Betulaceae, Fagaceae, Moraceae, and Salicaceae. This is the typical inflorescence of willow (Salix), cottonwood

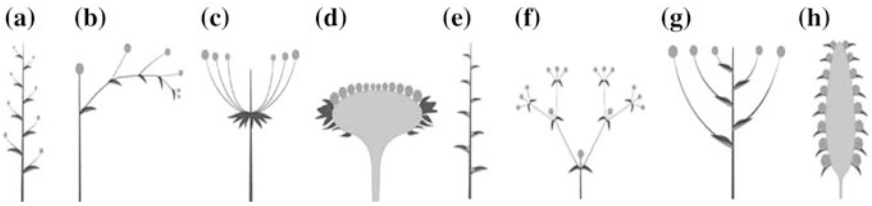


Fig. 6.41 Types of inflorescence (diagrammatic). **a** Raceme, **b** Uniparous cyme, **c** Umbel, **d** Capitulum, **e** Spike, **f** Biparous cyme, **g** Corymb, **h** Spadix

(Populus), oak (Quercus), alder (Alnus), and birch (Betula). All these species belong to a polyphyletic group of angiosperm families known as the Amentiferae; spadix, a thick, fleshy spike of unisexual, apetalous flowers, often surrounded by a vase-shaped or funnel-like modified leaf or spathe which is often brightly colored. The male flowers are typically clustered above the female flowers on an erect, phallus-like spike. This is the characteristic inflorescence of the arum family (Araceae).

There are a large number of flowers, which constitute pharmaceutically useful drugs. Flower drug chamomile is the dried flower heads of *Matricaria chamomilla*, *Chamaemelum nobile* of Asteraceae. Common hop or hop is derived from the female catkin flowers of *Humulus lupulus* of Cannabaceae. Santonin is derived from santonica, the unexpanded flower heads of *Artemisia maritima* var. *stechmanniana* of Asteraceae. Others refer to *A. cina* or *A. chamaemelifolia* as being the derivative species. Flowers of *Nelumbo nucifera* Nymphaeaceae contains lotusine, demethyl coclaurine, neferin, and nuciferine; it is both sedative and euphoric. Clove is the dried flower buds of *Eugenia caryophyllus* of the family Myrtaceae. Pyrethrum flower consists of the dried flower—heads of *Chrysanthemum cinerariaefolium*, an annual herb of the family Compositae. Passion flower (*Passiflora incarnata*, Passifloraceae) contains alkaloids, flavonoids, etc., and has been used to treat sleep disorders. Saffron is derived from the crimson stigmas of the flower of *Crocus sativus* of Iridaceae.

6.5.5 Fruit

Ovary develops and matures into fruit following fertilization while the fertilized ovules within the ovarian enclosure transform into seeds (Fig. 6.42). The covering of the mature fruit representing the ovary wall is called the pericarp. The pericarp is usually divisible into epicarp (outermost layer or epidermis), mesocarp (middle portion of the pericarp), and endocarp (inner most layer of the pericarp). The epicarp is usually a one cell thick layer, but in some cases may include one or more hypodermal layers as in colocynth. The mesocarp forms the bulk of the fruit and may be succulent or pithy, or it may consist of several layers of different types of cells, or may be composed of a spongy parenchyma. However, in all cases, the vascular strands ramify in the tissue of the mesocarp. The endocarp may consist of only one layer of cells or of several modified layers forming a thick woody structure. This woody structure forms a hard casing of the seeds as in cocoanut.

The external characters of a fruit are manifested on its epicarp. The epicarp frequently possesses stomata, usually in small numbers. Well-formed solitary crystals (prisms) of calcium oxalate occur in certain cells of the epicarp of coriander and vanilla. Characteristic cells with thickened walls occur in the epicarp of vanilla. The epicarp of some fruits remains covered with striated cuticles as in aniseed and caraway. Trichomes and hairs also frequently occur on the epicarp of many fruits

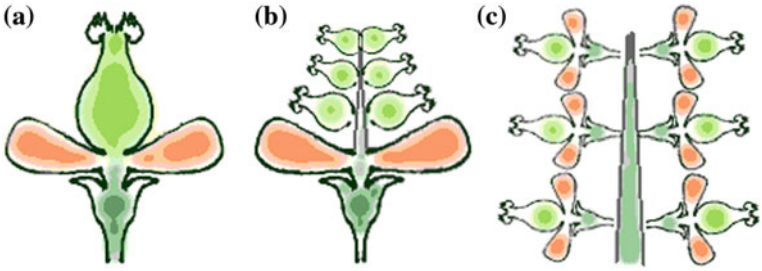


Fig. 6.42 Diagrammatic representation of how ovary of a flower with or without accessory parts (such as receptacle in case of apple, strawberry) develops and matures into fruit. **a** A flower with single ovary develops simple fruit (pea, lemon, banana); **b** a flower with multiple free carpels develops aggregate fruit (raspberry, blackberry); **c** the entire inflorescence develops into a single mass of fruit composite or multiple fruits (jack fruit, pineapple). *Source* www.backyardnature.net/frt_aggr.htm&h

particularly the young ones as in Chinese gooseberry or kiwi fruit (*Actinidia deliciosa*). Fruits are grouped into simple, aggregate, and composite or multiple fruits.

6.5.5.1 Types of Fruit

Simple Fruit

Simple fruit develops from single ovary of a flower with or without accessory parts. A simple fruit may be dry or fleshy. The dry simple fruits may be dehiscent (a. legume or pod of *Senna*, b. follicle of *Calotropis*, and c. capsule of *Stramonium*, opium poppy, cotton, etc.) or indehiscent (a caryopsis of rice, wheat and maize; b. cremocarp of anise, coriander, fennel, caraway, dill, etc.) when mature. Fleshy simple fruits are a. drupe and drupaceous (mango, prune or plum, palm coconut, etc.); b. berries (capsicum, orange, tomato, colocynth, guava, paw-paw, banana, etc.); c. pod (tamarind) (Fig. 6.43).

Aggregate Fruit

An aggregate fruit develops from single flower that has multiple carpels which are not joined together, i.e., each pistil contains one carpel and each pistil forms a fruitlet, and collectively the fruitlets are called an etaerio. Four types of aggregate fruits include etaerios of achenes (strawberry, rose, lotus, *Naravelia*, *Clematis* and *Ranunculus*,), follicles (*Calotropis*, *Magnolia*, *Michelia*, *periwinkle*, *Delphinium*, *Aconitum)*, drupelets (raspberry, dewberry and blackberry), and berries (*Annona*, *Artabotrys*, *Polyalthia)* (Fig. 6.44).

Composite or Multiple Fruit

If the entire inflorescence develops into a fruit, it is known as a multiple or composite fruit (Fig. 6.45). Each of the flowers of the inflorescence produces a fruit, but

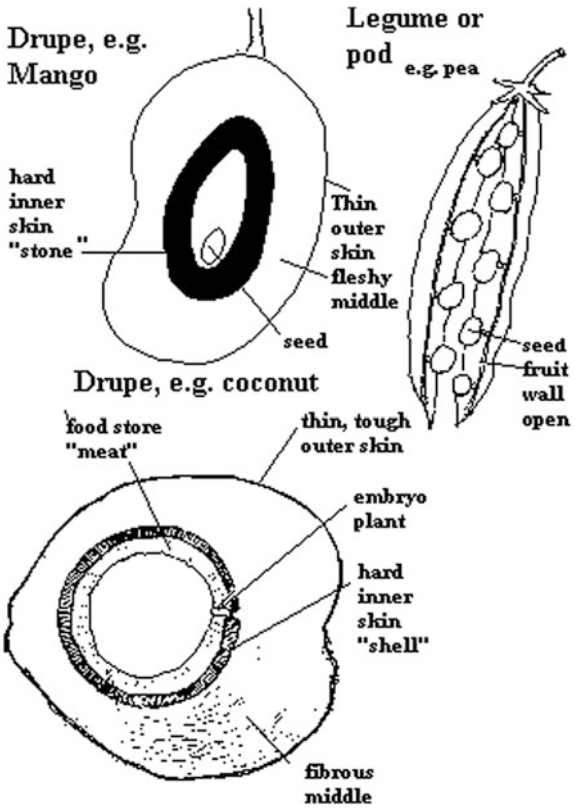


Fig. 6.43 Simple dehiscent and indehiscent fruits

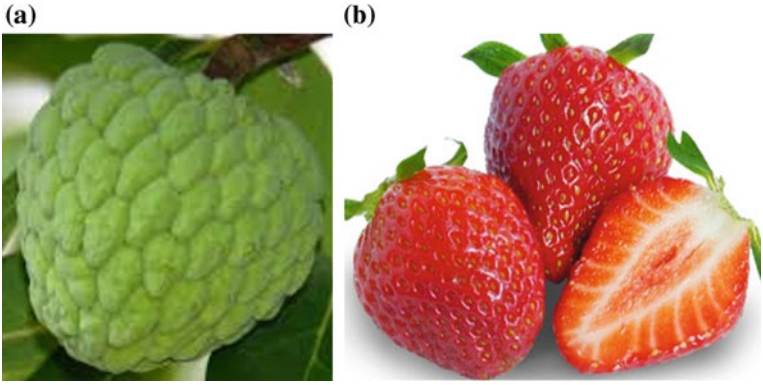


Fig. 6.44 Aggregate fruits: **a** Anona (an etaerio of berries), **b** Strawberry (an etaerio of achenes)

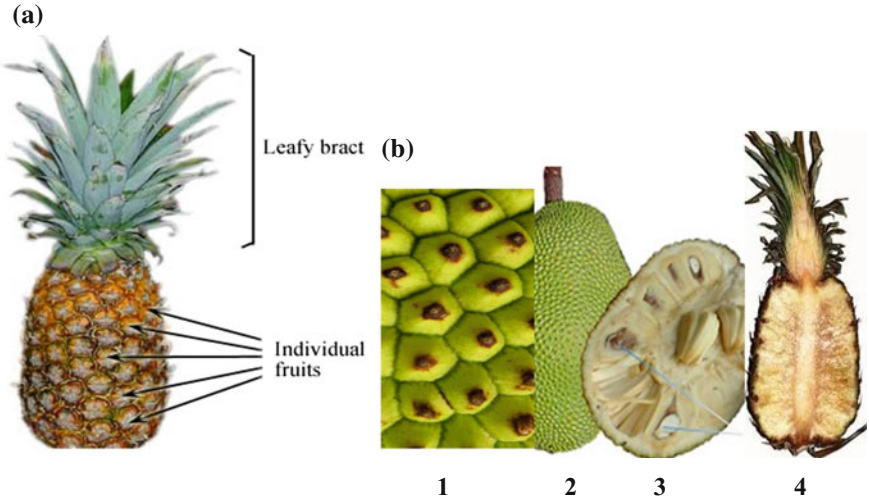


Fig. 6.45 Composite or multiple fruit **a** pineapple showing individual fruit visible as eye at the surface; **b** jackfruit: *1* styles of sessile female flowers transformed into spines, *2* intact fruit, *3* fruit in longitudinal section showing perianth, fleshy peduncle, and bladder like fruit with a single large seed, LS of pineapple showing fleshy axis and ovaries with receptacle, sepals, and bracts

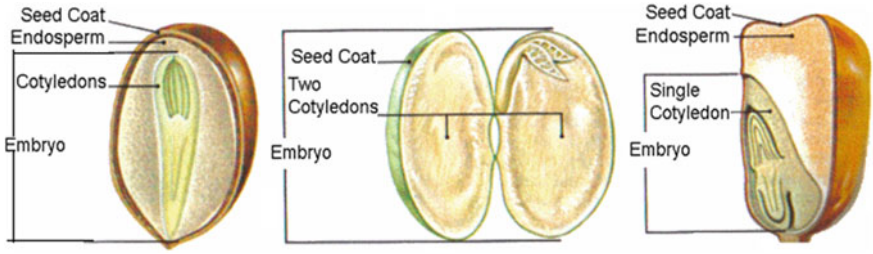
these all mature into a single mass to form the composite fruit. There are two common types of multiple fruits:

(i) Syconus—It develops from the hypanthodium inflorescence. After fertilization, the hollow receptacle becomes fleshy, e.g., fig, banyan, peepul (=*Ficus*).
(ii) Sorosis—It develops from spike, spadix, or catkin. In pineapple, the fruit develops from a spike, where the axis, the bract, and the perianth became fleshy and juicy. In jackfruit, fruit develop from spadix inflorescence, which bears sessile flowers. The female flowers have styles which are spines on the surface. The perianth, fleshy peduncle are edible and enclose a bladder like fruit with a single large seed. Pineapple, screw pine, and also mulberry are other examples of sorosis.

There are a large number of fruits, which constitute pharmaceutically and commercially useful drugs. Some of the examples are amla, anise, bael, bahera, bitter orange peel, *Capsicum*, caraway, cardamom, colocynth, coriander, cubebs, cumin, black cumin, dill, fennel, *Pedalium*, *Terminalia*, lemon peel, *Papaver*, *Senna* pod, star anise, tamarind, wormseed, etc.

Seed

Seeds are mature, fertilized ovules of the spermatophyta (gymnosperms and angiosperms) and serve as their dispersal and propagation units. Ovules are structures of seed plants containing the female gametophyte with the egg cell, all being surrounded by the nucellus and 1–2 integuments. In angiosperms, the double



Gymnosperm seed (Pine) Dicot seed (Bean) Monocot seed (Corn)

Fig. 6.46 Seed parts of pine, bean, and corn

fertilization results in formation of the diploid embryo (2n) and the triploid endosperm (3n).

Seeds gymnosperms are uncovered or naked because they lack ovary and those of angiosperms are covered or enclosed by ovary. Seeds of gymnosperms develop on the upper side of the scales that form their cones while angiospermic seeds develop within ovary. Seeds consist of three main parts, e.g., seed coat or testa, (2) embryo, and (3) endosperm (Fig. 6.46). The seed coat, or outer skin, protects embryo, endosperm nourishes the embryo until it can make its own food. The endosperm of a monocot contains one cotyledon, and that of a dicot has two cotyledons.

Embryo represents the young sporophyte, 2n in chromosome number, and develops as a result of fertilization. The mature embryo consists of cotyledons (seed leaves), hypocotyl (stem-like embryonic axis below the cotyledons), and radicle (embryonic root). Perisperm is diploid maternal food storage tissue originates from the nucellus in some species, e.g., *Beta vulgaris*, *Piper nigrum*, *Coffea arabica*, many Caryophyllales. Endosperm is food storage tissue, triploid (3n), result of double fertilization, 2/3 of the genome is of maternal origin. Endospermic seeds contain endosperm as food storage tissue, and the amount of endosperm in mature seeds is highly species-dependent and varies from an abundant endosperm layer as in tobacco (*Nicotiana tabaccum*) to a single layer as in ice plant (*Arabidopsis thaliana*). The cotyledons serve as sole food storage organs as in the non-endospermic seeds. During embryo development, the cotyledons absorb the food reserves from the endosperm. The endosperm is almost degraded in the mature seed, and the embryo is enclosed by the testa and the examples of non-endospermic seeds include rape (*Brassica napus*), and the legume family including pea (*Pisum sativum*), garden or French bean (*Phaseolus vulgaris*), soybean (*Glycine max*). The embryo of mature pea seeds of consists of the embryonic axis and the cotyledons. The fleshy storage cotyledons make up most of the seed's volume and weight. Most orchid seeds exhibit acotyledonous embryos and do not contain nutritional storage tissues or endosperm. Bean is non-endospermic seed with storage two cotyledons and the testa, castor bean is endospermic seeds with storage two cotyledons and the testa and wheat is endospermic seed with one cotyledon.

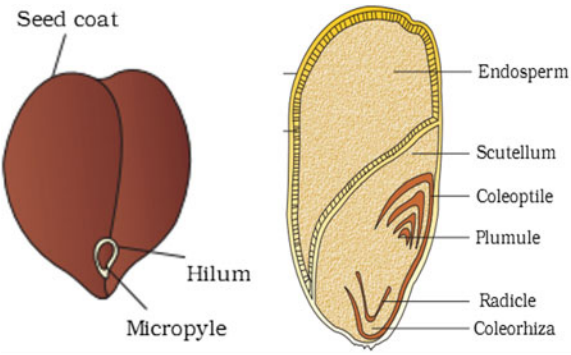


Fig. 6.47 Gram and rice seeds

Special Structural Features

The hilum on the seed is the point where the seed is attached to the ovary wall (Fig. 6.47). Funicular scar is seen on seed coat, and it marks the point at which the seed was attached via the funiculus to the ovary tissue. The Micropyle is a canal or hole in the coverings (seed coat) of the nucellus through which the pollen tube usually passes during fertilization. The micropylar seed end has been demonstrated to be the major entry point for water during tobacco seed imbibition and germination.

During germination the tobacco testa ruptures at the micropylar end and the radicle protrudes through the micropylar endosperm. Chalaza is the non-micropylar end of the seed; the base of an ovule, bearing an embryo sac surrounded by integuments. Raphe is seen as ridge on seed coat formed from adnate funiculus. Arillate is a general term for an outgrowth from the funiculus, seed coat or chalaza; or a fleshy seed coat. Aril is outgrowth of funiculus, raphe, or integuments; or fleshy integuments or seed coat, a sarcotesta. Arils probably often aid seed dispersal, by drawing attention to the seed after the fruit has dehisced, and by providing food as an attractant reward to the disperser. The aril of the nutmeg produces the spice mace and the seed itself is the nutmeg. Strophiole is the outgrowth of the hilum region which restricts water movement into and out of some seeds. In some hard-coated legume seeds, e.g., *Melilotus alba* and *Trigonella arabica*, a plug covering a special opening—the strophiolar cleft—must be loosened or removed before water can enter, and then only through this region. Strophiolate seed bears elongate aril or strophiole in the hilum region. Operculum refers to a dehiscent cap of a seed or a fruit that opens during germination. Carunculate seed is with an excrescent outgrowth from integuments near the hilum, as in Euphorbia. Fibrous seeds are with stringy or cord-like seed coat, as mace in Myristica. Funicular seed is seen with a persistent elongate funiculus attached to seed coat, as in Magnolia.

Drugs from Seeds

Seeds of Bitter almond, Black Mustard, Cardamom, Colchicum, Ispaghula, Kaladana, Linseed, Nutmeg, Nux-vomica, Physostigma, Psyllium, Strophanthus,

White mustard, etc. Have medicinal importance. Chaulmoogra oil from fresh seeds of *Hydnocarpus kurzii* of Flacourtiaceae and related species to treat skin diseases and leprosy; Croton oil, the dried ripe seeds of *Croton tiglium* contains the fatty croton oil which is one of the most powerful of purgatives; Psyllium, commercial psyllium is the seed of several of the fleaworts, e.g., French psyllium (*Plantago indica*), Spanish psyllium (*P. psyllium*), the East Indian product (*P. ovata*) are mild laxative; Strophanthus, dried ripe seeds of *Strophanthus kombe* and *S. hispidus* of Apocynaceae contain 8–10% of cardioglycoside drug, Strophanthus K, is used as a heart stimulant and about 30% of fixed oil. Their other constituents include kombic acid, the alkaloids, choline and trigonelline, resin, mucilage, and calcium oxalate. Castor bean (*Ricinus communis* of Euphorbiaceae) seeds are highly toxic to humans and many animals, ingestion of two beans can be lethal to humans. Castor seeds contain about 50% fixed oil and 26% protein. It also contains a crystalline principle, ricinine (0.2%), a toxin, ricin and an enzyme, lipase. Nux-vomica consists of the dried seeds (endospermic) of *Strychnos nux-vomica*, a small tree of Loganiaceae. The seed drug Nux-vomica contains the indole alkaloids, strychnine (about l.24%), and brucine (about 1.5%). It also contains caffeotannic acid, a glycoside, loganin, and a fixed oil. Cola seeds are obtained from *Cola vera* a large handsome tree of Sterculiaceae. The principal constituent of Cola seed is caffeine (1–2.5%). Other constituents include a crystalline compound, kolatin (0.75%), traces of theobromine, and oxidase enzyme, fat, sugar and abundant starch. Peanut consists of the seeds of *Arachis hypogoea* of Papilionaceae. The chief constituents of peanut include 50–60% fixed oil, 25–30% proteins and 15–20% starch. The brown covering of the seeds are rich in vitamins and minerals. Soybeans consist of the dried seeds of Glycine max Papilionaceae. The seeds contain ∼18% fixed oil, 38% proteins and an enzyme, urease. Linseed is the dried ripe seed of *Linum usitatissimum* of Linaceae. The chief constituents of Linseed include fixed oil (30–40%), proteins (2.55%), mucilage (6%), and a small quantity of linamarin (a cyanogenetic glycoside). Nutmegs consist of the dried kernels of the seeds of *Myristica fragrans*, an evergreen tree of Myristicaceae. Nutmeg principally contains volatile oil (5–15%) and fat (30–40%). It also contains phytosterin, starch, amylodextrin, coloring matters, and a saponin.

6.5.6 Bark and wood

Bark refers to all the tissues outside of the vascular cambium of stems and roots of trees, woody vines, and shrubs. Bark overlays the wood in a mature tree (Fig. 6.48). Cambium tissue produces xylem on the inside and phloem, the primary bark tissue, on its exterior side. Phloem tissue contains phloem parenchyma, bast fibers, companion cells, and sieve tubes. The sieve elements are the main channel for downward movement of sap and nutrients from the leaves contrary to the

upward rise of water from the roots in the xylem. The layer of physiologically active tissue adjacent to the cambium is known as the inner bark and is generally relatively thin and light colored. As subsequent layers of phloem are laid down year by year, the outer layers become crushed and compressed, and the sieve elements and similar structures collapse. This tissue then ceases to take part in active physiological processes and is transformed into the relatively inert, dark outer bark that comprises the bulk of most tree barks. The rifted or scaly outermost layer of such bark on mature trees is then called the rhytidome. The structure of bark is further complicated by the presence of a second cambial layer within the bark called the phellogen or cork cambium. Cork is produced by cork cambium and contributes appreciably to the structure of the outer bark. Cork and cork cambium together constitute the periderm. The innermost layer of periderm is normally considered as the boundary between the inner and outer bark. A number of other types of auxiliary tissues, e.g., lignified sclerenchyma and medullary ray parenchyma, are also found in bark.

6.5.6.1 Morphology of Bark

Bark is a living cylinder of tissue which, as the tree grows, periodically produces a new inner layer. The outer bark is acted on by external weathering processes and tangential strain to produce the fissures and ridges of the surface. The surface pattern of the bark is a visual summation of the surface configurations, the sloughing pattern, the texture, and the color. The external tissues of older barks often have a rugged and scaly appearance due to lenticels, cracks and fissures, wrinkles and furrows, exfoliations and formation of rhytidoma. Some of the common features include: a. Ironbark, b. Fracture, c. Tessellation, d. Furrowed,

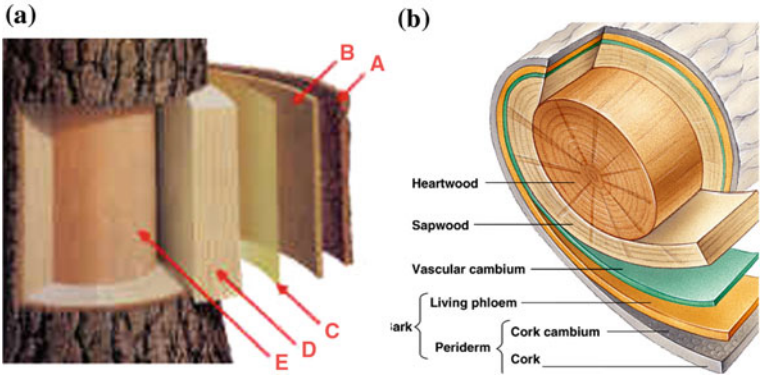


Fig. 6.48 Schematic diagram of the anatomy of a tree showing superimposition of different tissue layers from outward to inward. **a** Side *A* outer bark or periderm, *B* inner bark or phloem, *C* cambium cell layer, *D* sapwood, *E* heartwood. **b** Top view: periderm (cork and cork cambium), bark (periderm and living phloem), sapwood and heartwood. *Source* https://www.arborday.org/trees/treeguide/anatomy.cfm/ [Link] Anatomy of a Tree

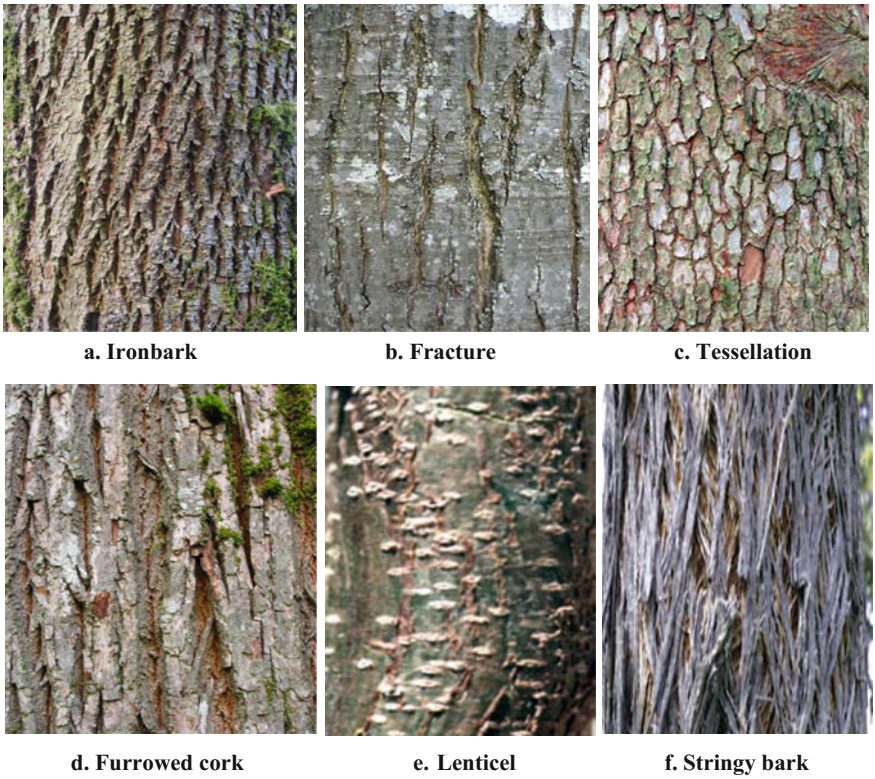


Fig. 6.49 Different bark features: **a** Ironbark, **b** fracture, **c** tesselation, **d** furrowed cork, **e** lenticel, and **f** stringy bark. *Source* http://www.americanforests.org/magazine/article/the-language-of-bark/#comment-47251

e. Lenticel, and f. Stringy bark (Fig. 6.49a–f). Ironbark is perhaps the easiest bark to recognize. It is rough, hard, and compact. As a tree increases in girth, great tension on the bark can cause fractures, which can be either vertical or horizontal. Tessellation happens when the bark fractures to form flakes or plates, sometimes large plates with deep furrows. Oak and a number of other trees have deeply furrowed bark with thick accumulation of cork cells. Lenticel is small, oval, rounded spots upon the trunk or branch a tree, from which the underlying tissues may be protrudent or cuppy. Lenticels are usually horizontal. Stringy bark has many dangling fiber strips.

6.5.6.2 Flat Barks

Flat barks are thick in long pieces, dried under pressure, and thus the finished product does not undergo any shrinkage or curvature and remain flat. This shape is

commonly found in cases of *Cinchona*, *Quillaia*and *Cassia* barks. Curved bark is only slightly concave on the inner side. Recurved when the concavity occurs on the outer side, e.g., *Terminalia arjuna*. Channeled where the curvature on the inner side is deep enough to form a trough, e.g., *Terminalia arjuna*; single quill bark is so deeply concave on the inner side that the edges of the bark nearly overlap; double quill bark is formed when both edges separately in rolled and compound quill, when single or double quills are packed on inside the other, e.g., Ceylon Cinnamon. The inner surface of the bark often possesses characteristic features, which are of diagnostic value. Shrinkage due to drying results in the production of parallel longitudinal ridges on the inner side, termed striations, which are characteristic of many barks. Occasionally, longitudinal shrinkage produces parallel transverse ridges, known as corrugations, as in *Cascara*.

6.5.6.3 Fractures of Barks

Dried barks break into pieces when subjected to pressure. The behavior of the barks when broken transversely toward the pressure applied and the appearance of the broken surfaces are referred to as their fracture. It gives an idea about the nature of tissues present. Fracture is one of the most useful diagnostic characteristics of the barks. Fractures may be short, splintery, fibrous, horny, granular, brittle, flexible, smooth, even or uneven, resinous, laminated etc. Fractures of the barks may be complete or they may be incomplete. Depending on the type of constituents present in the bark, the fractured surface may appear mealy (when it contains abundant starch) or resinous (when large amount of resin is present) or waxy (due to presence of larger quantities of resins, waxes, gums, and mucilage in the bark).

6.5.6.4 Shape of Barks

The natural curvature of the barks changes when they are removed from the tree and dried. Depending on the size and thickness of the bark removed, a bark may assume flat, curved, recurved, channeled, quilled, doubled, and compound quilled (Fig. 6.50).

6.5.6.5 External Characters

The common external characters of the bark include the following:

(a) Lenticels: These are slightly raised small cracks or openings in the bark through which gases can pass across the impervious phellem into and out of the trunk or branch. They are formed by porous tissue consisting of cells with large intercellular spaces in the periderm of the bark of woody stems and roots of dicotyledonous flowering plants. Lenticels may be round, oval, or elliptical in

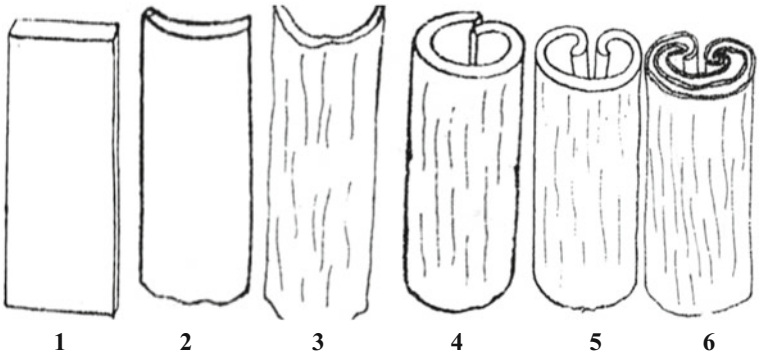


Fig. 6.50 Shape of barks. *1* flat, *2* curved, *3* channeled, *4* single quill, *5* double quill, *6* compound double quill

shape (Fig. 6.51). The shape of lenticels is one of the characters used for tree identification. As stems and roots mature lenticel development continues in the new periderm. Lenticels are also present in pneumatophorous roots (respiratory roots), on fruits (apples and pears), and on potato tubers.

(b) Exfoliates: Exfoliation means the loss of leaves or, in some cases, pieces of bark from a plant. Exfoliate are formed on many barks due to frequent flaking off of the corky layer of the bark, exposing the cortical layer beneath, e.g., Cinchona and Cinnamon barks. In exfoliate or peeling bark, there occur thick-walled cells alternating with thin-walled cells which causes barks to separate like thin wrappers, peeling or exfoliating from where a layer breaks (*Bursera*, *Prunus*, *Betula*). Peeling barks of eucalyptus species occur because

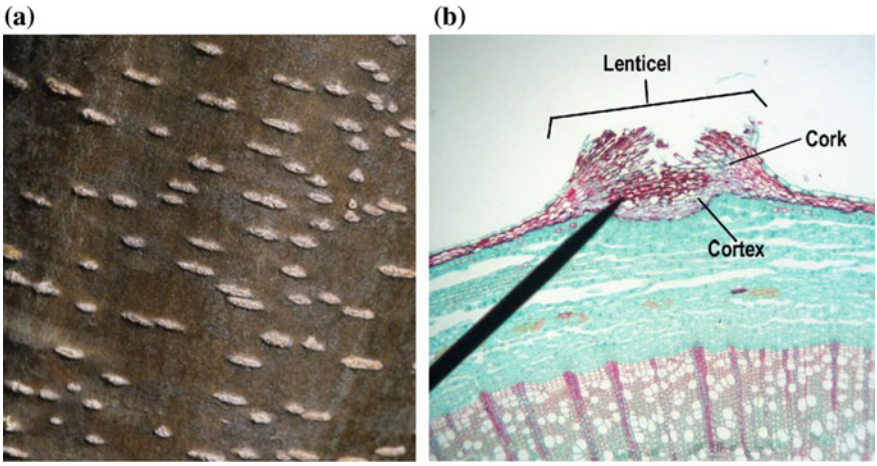


Fig. 6.51 Lenticel on the bark surface of the Speckled alder (*Alnus rugosa*) (**a**); and lenticel as seen in TS of the stem (**b**)

layers of bark separate where there is thin-walled phloem parenchyma. Shagbark hickory (*Carya ovata*) has peeling strips (scaling) of fibrous bark. Species of *Melaleuca* and *Callistemon* (family Myrtaceae) often have exfoliating layers like paper. Some species of legumes also have peeling bark.

(c) Cracks and fissures—These are produced on the surface of the bark due to continued increase in the girth of the plant and lack of elasticity in the dead tissues of the bark. These cracks and fissures (small cracks extending into the inner tissues) are often characteristics of many bark drugs, e.g., cracks with clean cut edges occur in *Cinchona succirubra* bark, but with thickened, recurved edges in that of *Cinchona officinalis*. Many trees with fissured bark have well-developed in the inner bark phloem or bast fibers, which give the trunk a very strong cover, are widely used making cordage, paper as well as in surgical dressing. Fibrous barks are not necessarily fissured, as in many species of figs (*Ficus*).

(d) Warts develop as small circular dusty patches in the cork of older barks, such as that of *Cinchona succirubra*.

(e) Wrinkles and furrows are formed on the outer surface of most barks during drying due to shrinkage of the softer tissues transversely. The cork oak (*Quercus suber*) and a number of other trees (*Cussonia spicata*, *Erythrina latissima*, and *Phellodendron*) have deeply furrowed bark with thick accumulation of cork cells. These cork cells tend to have thin-walls and are filled with air. Corky outer bark may also appear in longitudinal arrangements or wings (*Casuarina*, *Aristolochia*, and *Zanthoxylum*).

(f) Epiphytes include the lichens, liverworts, and mosses, which are often present on the outer surface of many barks which have not been pealed or cleaned. They provide important additional characters for the identification some bark drugs.

(g) Ring bark, where a stem has concentric successive periderms (entirely cylindrical), a tight or smooth bark can develop.

(h) Scaly bark, where a stem has discontinuous, overlapping successive periderms, patches of bark will form and can be shed. This is generally termed a scaly bark.

(i) Smooth barks can be smooth and very glossy to dull. Generally, these have a very thin outer bark.

(j) Green stems almost always are able to capture sufficient sunlight when development of the opaque initial periderm is delayed or totally suppressed. A stem can contribute significantly to total carbon uptake of the plant only if stomates are present at a substantial density and can remain functional over several years.

(k) Stem succulents such as cacti and euphorbs have a long delay in the initiation of periderm. These stems do not tear or split because the epidermis undergoes extra cell divisions during its formation for increasing the surface area. Instead, periderm formation occurs primarily in response to stress and injury, e.g., sun damage along rib margins. When periderm forms, it typically arises from the

outermost layer of cortex and requires a long time to encircle the axis. In many arborescent cacti, for example, only the trunk is fully covered by scaly bark.

(l) Photosynthetic old stems such as palo verdes (*Cercidium* and *Parkinsonia aculeata*), over many years experience cell divisions of the epidermis, cortex, and phloem, thereby increasing stem surface area while stem circumference increases without disturbing the operations of the stomates. Even a fully mature palo verde may have very little bark formation on the trunk. Many shrubs of desert and semiarid habitats have photosynthetic stems that remain green for several years before developing the initial periderm.

(m) Corky wings—One diagnostic character is the presence of corky wings on young stems. In some cases, wings are due to stimulation of localized phellogens along a stem angle, as in winged euonymus (*Euonymus alata*). Wings also occur on young stems of sweet gum (*Liquidambar*). Longitudinal splitting is the cause of stem wings in certain species of elm (*Ulmus*).

(n) Monocotyledonous periderm—In certain arborescent species, e.g., *Cordyline terminalis*, *Dracaena draco*, and *Yucca*, segments of suberized cells appear but without having a special cambium. This is termed storied cork. *Aloe bainesii* and other arborescent aloes have a scaly to exfoliating type of surface layers. In palms, the outer cells of the trunks become heavily lignified, and a few palm species (*Livistona*) also have suberin deposited in surface cell walls. No monocotyledon has a true periderm as found in dicotyledons and gymnosperms.

(o) Bark armature—Bark on old stems and trunks may have formidable armature in the form of heavy, persistent bark prickles (also called bark emergences). Examples are found in Bombacaceae, *Zanthoxylum*, and certain Sapotaceae. Stipular spines may also persist on old stems. The majority of woody plants have alkaloids, tannins, resins, latex in bark cells, and tissues.

Stem barks differ from root barks in color, thickness, shape, and outer surface contents, e.g., outer surface is light in color than the inner in stem bark while in root both outer and inner surfaces are same in color, stem bark surface contains epiphytes and lenticels but these are absent in root barks, stem barks are thicker than root barks, stem barks may be flat, curved or quilled while root barks are irregularly quilled or twisted.

Bark has a long history of utility and products from bark include food stuffs, flavorings, tannins, dyes, gums, resin, latex, antibiotics, medicinals, various hallucinatory chemicals, fish and arrow poisons, fibers, and cork. Among the commercial products of therapeutic importance made from bark are cinnamon, quinine (from the bark of *Cinchona*), aspirin (from the bark of willow trees), the powerful aphrodisiac, yohimbine, and the root beer flavoring, sassafras. There are a large number of barks, which constitute pharmaceutically and commercially useful drugs and are reported to be used for treating inflammation, dyspepsia, flattulence, colic, helminthiasis, vomiting, skin diseases, leprosy, diabetes, and rheumatism (Sumy et al. 2000). The bark is bitter, astringent, thermogenic, anti-inflammatory, digestive, carminative, laxative, depurative, anthelmintic, repulsive, and urinary

astringent. It is useful in vitiated conditions of pitta and cough, hemorrhage (Varriers 1996), hydrocele (Shrivastava and Jain 2005). Barks of Arjuna, Ashoka, Cascara, Cassia, Cinchona, Cinnamon, Kurchi, Quillia, Wild cherry, etc., are medicinally important.

The barks of various *Ficus* species (e.g., *F. racemosa*, *F. virens*, *F. religiosa*, *F. benghalensis*) individually or in combination are considered to be very effective in various treatments, such as diabetes, skin diseases, ulcers, and nervous disorders (Gayathri and Kannabiran 2008, Babu et al. 2010).

6.5.6.6 Wood

Wood represents the central harder part of all shrubs and trees inside the secondary cambium ring. Wood consists of mainly the secondary xylem tissues—tracheids, vessels, wood fibers, wood parenchyma, and medullary ray parenchyma. Tracheids form the great bulk of the woods of the Conifers, e.g., *Pinus*, *Ephedra* and *Alnus*; vessels are characteristic of the Angiosperm woods and are absent in Conifers. Tracheids and vessels occur in various sizes with characteristic secondary thickenings of walls in various groups of wood. Wood parenchyma occurs in association with the vessels in most woods, whereas the medullary ray parenchyma transverses the wood tissue forming the medullary rays in a radiating pattern. Fibers constitute the major bulk of the wood and determine the texture of the wood (Fig. 6.52).

With the continuous formation of secondary xylem tissues by the cambium, the primary or original xylem tissues are gradually pushed toward the center, become more compact and die due to over congestion as well as accumulation of tannins,

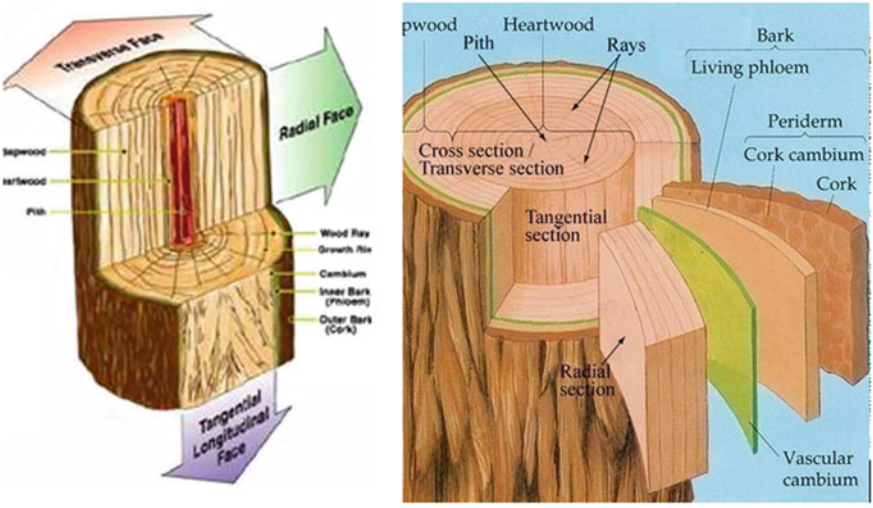


Fig. 6.52 Anatomy of a tree trunk showing plane of sections and tissue arrangements in wood and bark in transverse, radial, and tangential surfaces

oils, gums, resins, etc., and formation of plugging tyloses (balloon-like ingrowths) in their cavities. These dead xylem tissues give rise to the hard, durable, and densely colored central wood, called the heartwood and provide mechanical support to the plant. The outer region consisting of the newly formed secondary xylem tissues, which are living, lighter in color and comparatively softer in texture, constitute the sapwood. This part of the wood is used by the plant for conduction of water and salt solutions from the root to the leaf.

Woods used pharmaceutically are obtained both from the heart wood and sapwood, but the great bulk comes from the heartwood. Examples of such woods include: Deal wood from *Pinus sylvestris* and *Picea excelsa*, Quassia wood from *Picrasma excelsa*, Guaiacum wood from *Guaiacum officinale*, Red Sandalwood from *Pterocarpus santalinus*, Sandalwood from *Santalum album* and Agarwood from *Aquillaria malaccensis*.

6.5.6.7 Drugs from Bark and Wood

Drugs from Bark

Cascara is obtained from the reddish-brown bark of *Rhamnus purshiana* of Rhamnaceae. It is as a tonic and laxative. Cinnamon consists of the dried inner bark of the shoots of *Cinnamomum zeylanicum* of Lauraceae. Cinnamon is chiefly used as a carminative and flavoring agent. Cinnamon contains 0.5–6.0% of volatile oil, the chief constituent of which is cinnamic aldehyde (60–70%) and eugenol (4%), tannin, and mucilage. It possesses astringent and antibiotic properties. Curare is poisonous extract from the bark, roots, stems, and tendrils of various woody lianas like *Strychnas toxifera*, *Chondodendron tomentosum* and species of *Abuta* and *Cocculus* as well as other species. Curare contains several alkaloids, e.g., curarine, which has now been available to medicine for use in shock therapy, and as an ideal muscle relaxant. Curarine is also used for chronic spastic conditions, in surgical operations and tetanus and as a powerful sedative. Quinine, an antimalarial alkaloid drug, is obtained from the hard thick bark of several tree species of the genus *Cinchona* of South America such as *C. calisaya*, *C. officinalis*, *C. ledgeriana,* and *C. succcirubra*. In addition to its use in the treatment of malaria, it is valuable as a tonic and antiseptic and in the treatment of fevers. Over 29 other alkaloids have been isolated from the bark, including cinchonidine, cinchonine, and quinidine. All of these are useful in medicine. Totaquina is a standard mixture of all of these alkaloids. Slippery elm is derived from the inner bark of *Ulmus rubra*. It contains mucilage and is used for its soothing effect on inflamed tissues, either in the crude state or in the form of lozenges.

Drugs from Stem and Wood

Ephedrine is an alkaloid from the low-growing shrub Asiatic *Ephedra sinica*., *E. equisetina,* and other species of the same genus. The drug is extracted from the entire woody plant. In modern times, it has been used in the treatment of colds, asthma, hay fever, and other medical purposes. Guiacum is a hard resin that exudes

naturally from the stems of the lignum vitae trees, *Guaiacum officinale* and *G. sanctum*. It hardens into round, glassy greenish-brown tears. It is acquired from incisions, from the cut ends of logs or from pieces of the wood. Gum guaiac is used as a stimulant and laxative. Quassia may be obtained from two different sources, e.g., Jamaican quassia, *Picrasma excelsa*, and Surinam quassia, *Quassia amara*. Quassia is transported in the form of billets, and the drug is extracted by preparing an effusion of chips or shavings. It is very bitter to the taste and is used as a tonic and in the treatment of dyspepsia and malaria. It is also an insecticide. In the wood, a share of 0.09–0.17% of quassin and 0.05–0.11% of neoquassin was detected in Costa Rican plants. Quassin is one of the bitterest substances found in nature.

6.5.7 Root

Roots, which constitute drugs, are usually the strongly developed primary (tap) roots, although many secondary roots and root system sometimes produce some important root drugs. Roots bear no leaves, scales, or buds. The only appendage present on the roots is the lateral branch roots, which are similar in construction to the main root. Thus, there is no external scar of leaf or scale on the roots. The outer surface of the thick or main roots sometimes possesses remains of the bases of the branch roots or their scars or scattered rootlets. Barks of the old thick roots bear cracks and fissures like those of the aerial stem barks.

6.5.7.1 Internal Structure of Root

The transversely cut surface of a root reveals characteristic features by which a monocotyledonous root can be distinguished from a dicotyledonous one. In the dicotyledons, to which most root drugs belong, there is a central woody core surrounded by the cambium, a cylinder of secondary phloem, and an external layer of cork. In monocotyledons, central pith is usually present and is often composed of thick-walled lignified cells; the xylem is porous and a cortex is present. However, all roots are externally covered by a piliferous layer. The major part of the root is made up of parenchymatous cortex. Internal to the cortex is a well-developed endodermis. The stele is surrounded by a single layer of pericycle and has alternating bundles of xylem and phloem on different radii, arranged in a circle. The xylem bundles frequently develop until they meet at the center of the root, forming a rod-shaped mass of xylem (Fig. 6.53).

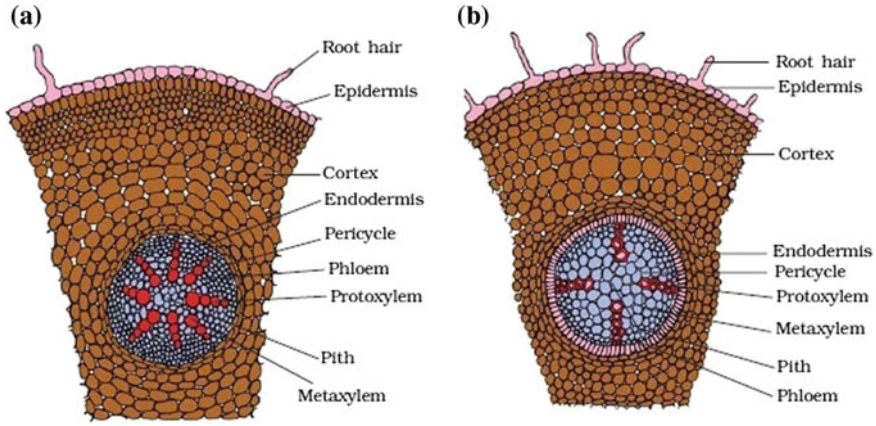


Fig. 6.53 Transverse section of **a** monocot and **b** dicot roots showing their internal structure

6.5.7.2 Root Drugs

Roots and Rhizomes from Aconite, Ashwagandha, Calamus, Calumba, Colchicum corm, Dioscorea, Galanga, Garlic, Gention, Ginger, Ginseng, Glycyrrhiza, Podophyllum, Ipecac, Ipomoea, Jalap, Jatamansi, Rauwolfia, Rhubarb, Sassurea, Senega, Shatavari, Turmeric, Valerian, Squill, etc., are sources of many drugs.

Aconite, Belladonna, Calumba, Dandelion, Ipecacuanha, Jalap, Rauwolfia, Sarsaparilla, and Senega are some of the important root drugs. Some of them are described below in the form of Monographs as representative examples for the students so that they can also describe other root drugs.

Aconite is obtained from the tuberous roots of the monkshood, *Aconitum napellus*. The plant is a native of the Pyrenees, Alps, and other mountainous regions of Asia and Europe. It is cultivated in temperate regions both as an ornamental and as a drug plant. At first the leaves and flowering shoots were utilized, but later only the roots were used. These are collected in the autumn and dried. Aconitine is the most important of the several alkaloids that are present. It is used externally for neuralgia and arthritis, and internally to relieve fever and pain.

Colchicum is obtained from the dried corms of the meadow saffron, *Colchicum autumnale*. It is a perennial tulip like herb of Europe and Northern Africa. It possesses an alkaloid, colchicine, which is used in the treatment of arthritis and gout. Fresh roots seeds are also used to some extent.

Gentian (bitter root) is prepared from *Gentiana lutea*, a tall perennial herb with striking orange-yellow flowers. Gentian is common in the mountains of Central Europe. The rhizomes and roots are dug out in the fall, sliced, and dried. They contain several glucosides that are valuable as a tonic for they can be used with iron salts.

Goldenseal, *Hydrastis canadensis*, was formerly common in the woods of Eastern North America. The Amerindians and European settlers used it as a

remedy. The roots and rhizomes contain several alkaloids that may be used as a tonic and for the treatment of catarrh and other inflamed mucous membranes.

Ginseng has been used in China since ancient times to cure an array of diseases. True ginseng, *Panax schinseng*, is a plant of Eastern Asia. Large quantities of American ginseng, *Panax quinquefolium*, have been grown in recent years. In America, ginseng is used as a stimulant and stomachic.

Ipecac may be obtained from several species, but the main source consists of the dried rhizome and roots of *Cephaelis ipecacuanha*. The main ingredient is emetin, a white, bitter, colorless alkaloid. Ipecac is used as a diaphoretic emetic and expectorant. It is valuable in the treatment of amebic dysentery and pyorrhea.

Jalap is a resinous drug obtained from the tubers of *Exogonium purya*, a twining, morning glory-like vine of the woodlands of eastern Mexico. The plant has been cultivated in Mexico, Jamaica, and India. The roots are collected and dried over fires. Jalap is used as a purgative.

Licorice is known from ancient times. The plant, *Glycyrrhiza glabra*, is a perennial herb that grows wild in Southern Europe and Western and Central Asia. The roots are dried in sheds for several months and are shipped in cylindrical pieces. Licorice is used in medicine as a demulcent and expectorant and to disguise the flavor of medicinal preparations. It has a compound, glycyrrhizin that is 50-times sweeter than sugar.

Podophyllum is obtained from the roots of Mandrake or May Apple, *Podophyllum pellatum*. The drug podophyllum has been used in rural eastern United States as an emetic and cathartic. Roots are collected in the autumn or spring and are cut into cylindrical segments and carefully dried. They contain a resin that is the source of the cathartic. East Indian podophyllum is obtained from *Podopjhyllum emodi* from the Himalayas.

Rhubarb drug is obtained from two shrubs *Rheum officinale* and *R. palmatum*. The rhizomes and roots are dug and cut into short pieces or slices, threaded on a string and dried in the sun or in kilns. Rhubarb is used as a tonic and laxative and for indigestion. East Indian rhubarb is from *Rheum emodi*.

Squills are obtained from the white variety of sea onion, *Urginea maritime*. The plant is native of the seacoasts of the Mediterranean and has come under cultivation. The bulbs are dug up and the outer scales removed. The fleshy inner scales are then sliced and dried. Several glucosides are present. The drug is used as an expectorant and stimulant. A red variety contains toxic substances that render it useful as a raticide.

Senega snakeroot or milkwort, *Polygala senega*, is a small herbaceous perennial of Eastern North America. It is the source of a glucosidal drug obtained from the dried roots. The common name was derived because Senega or Seneca Indians used the plant as a cure for snakebites. Senega is used as an expectorant, emetic, and stimulant.

Valerian is derived from the dried rhizomes and roots of the garden heliotrope, *Valeriana officinalis*. Native to Eurasia, it has long been cultivated in the USA as an ornamental. It contains an essential oil that is used to relieve nervous afflictions, pain, coughing, and hysteria.

Aconite consists of the dried tuberous roots of Aconitum nczpellus Linn., a perennial herb of the family Ranunculaceae. Aconite root principally contains three closely related alkaloids, namely aconitine, picraconitine, and aconine. It also contains small amounts of other alkaloids, aconic acid, and starch. Tinctures of Aconite and aconitine are used externally in certain forms of neuralgia and rheumatism, and internally in small doses in cases of fever and pain.

Belladonna root consists of the dried roots and rootstocks of *Atropa belladonna* Linn. of the family Solanaceae. Belladonna root contains tropane alkaloids, the principal one being hyoscyamine. It also contains a small amount of hyoscine. Besides these, it contains a crystalline fluorescent compound, Beta-methyl aesculetin, tannin, starch, and calcium oxalate. Belladonna out extract is externally used as a local anesthetic and anodyne. Internally, it is used to check sweating and other glandular secretions, as a sedative, antispasmodic, and mydriatic agent.

Gentian consists of the dried roots and rhizomes of *Gentiana lutea*, a herbaceous perennial plant of the family Gentianaceac. Gentian contains a large number of bitter glycosides, which include gentiopicrin, gentiamarin, gentiin. It also contains free sugars, gentianose and sucrose, enzymes, 2 a yellow coloring matter, pectin and an oil. Gentian is used as a very favorite bitter tonic.

Ipecac consists of the dried, enlarged adventitious roots and slender rhizomes of *Cephaelis ipecacuartha* of the family Rubiaceae. Ipecacuanha contains 2–5% of total alkaloids, which include emetine (about 70%), cephaeline (about 30%), psychotrine, methyl psychotrine, and emetamine. It also contains a glycoside, ipecacuanhic acid, starch, and calcium oxalate. The drug is mainly used as an expectorant and emetic, and as a remedy for amebic dysentery. It also possesses diaphoretic and cholagogue properties.

Jalap consists of the dried tubercules of Ipomoea purga Hayne, a climbing, twining plant of the family Convolvulaceae. Jalap principally contains a glycosidal resin (8–20%). Other constituents include mannitol, sugars, starch, Beta-methyl aesculetin, and calcium oxalate. Jalap is used as a hydrogogue cathartic. In smaller doses, it acts as a laxative and in larger doses it causes active purgation.

Rauwolfia consists of the dried roots of *Rauvolfia serpentina*, a large shrub of the family Apocynaceae. Rauwolfia contains 1.2–1.4% of total indole alkaloids, the most important of which are reserpine, deserpidine, and rescinnamine. Its other constituents include resinous matter, fatty acids, unsaturated alcohols, dextrose, and sucrose. Rauvolfia is used in reducing high blood pressure and as a sedative in the treatment of insomnia, anxiety, insanity, and certain other neuropsychiatric disorders.

6.5.8 Rhizome

Rhizomes are thickened stems growing horizontally, vertically, or obliquely under the surface of the soil. They possess distinct nodes and internodes and bear scale leaves at the nodes. Occasional buds occur in the axils of the scale leaves. They

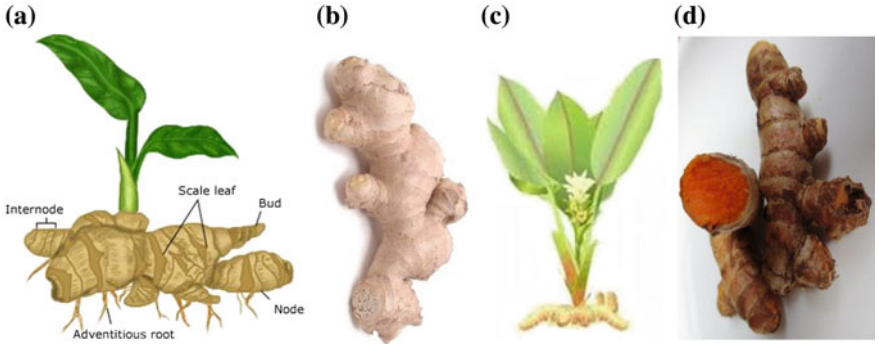


Fig. 6.54 Rhizomes of *Zingiber officinale* (**a**, **b**) and *Curcuma longa* (**c**, **d**)

bear slender adventitious roots on their under surface. Rhizomes may be unbranched bearing a bud at the growing end, or branched, each branch ending in a terminal bud. Examples of rhizome drugs include Arnica, Ginger, Hydrastis, Liquorice, Male Fern, Podophyllum, Rhubarb, Turmeric, and Valerian (Fig. 6.54).

The upper surface of the horizontally growing rhizomes is often marked with scars of fallen aerial leaves, as in Oris. The lower surface of the horizontal rhizomes and the whole surface of vertical and oblique rhizomes bear roots and small circular scars of fallen roots

6.5.8.1 Internal Structure of Rhizome

Rhizomes have a general internal structure similar to that o aerial stems (Fig. 6.55). But they do not have any well-developed column of xylem tissue in the form of a central wood, a useful character that helps to distinguish rhizomes from roots. The characteristic features of the transversely cut surface of a rhizome can be successfully employed to distinguish between drugs derived from different groups of plants. Drugs of cryptogamic rhizomes show number of separate steles; the dicotyledonous rhizomes have circle of vascular bundles and central pith and in monocotyledonous rhizomes the vascular bundles are scattered throughout the stele and cortex, and an endodermis is evident.

In the unpeeled rhizomes, either an epidermis or a few layers of thin-walled cork cells constitute the outer part. The cortex usually consists of thin-walled parenchyma cells containing food reserves like starch, inulin, and hesperidin. The vascular bundles in the stele are collateral and consist of both xylem and phloem. They are variously distributed in the ground tissue depending on the group of the plants. There are a large number of rhizomes, which constitute pharmaceutically and commercially useful drugs. Some of them are described below.

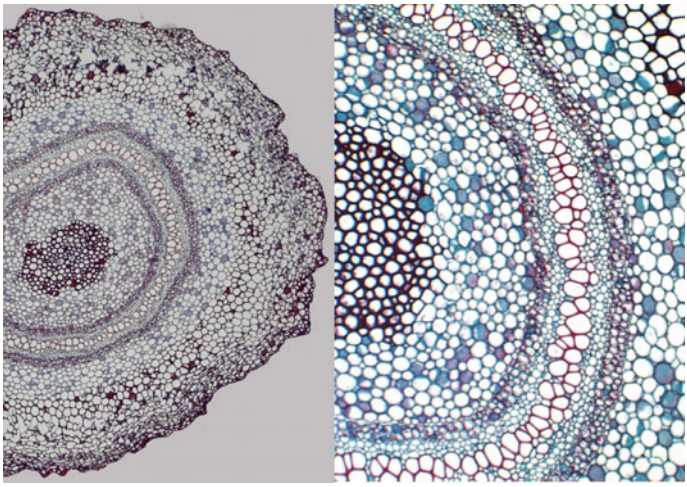


Fig. 6.55 Internal structure of rhizome

6.5.8.2 Drugs from Rhizome

Ginger consists of the dried rhizomes of cultivated *Zingiber officinale* of Zingiberaceae.

Ginger contains 5–8% resinous substances, the chief constituent of which is gingerol. Ginger also contains 0.25–3.0% volatile oil, which contains zingiberene, citral, borneol, camphene, and phellandrene. It also contains 50% starch, 2–3% proteins, and a small amount of sugar. Ginger is used as a carminative and aromatic stimulant. It is also used as a condiment.

Licorice, Liquorice Root, Glycyrrhiza, Glycyrrhizae Radix: Liquorice is derived from the stolons and roots of Glycyrrhiza glabra Linn. and other species of the genus Glycyrrhiza (Family Papilionaceae).

Liquorice contains 5–7% of glycyrrhizin (a sweet principle made up of potassium and calcium salts of glycyrrhizic acid). It also contains glucose, sucrose, a bitter principle, starch fat, and calcium oxalate. Liquorice is used as a demulcent and expectorant. It is also used in the treatment of gastric and duodenal ulcers.

Aspidium: Male Fern, Filix Mas, Male Fern Rhizome, Aspidium consists of the rhizome, frond bases and apical buds of Dryopteris fihix-mas (Linn.) Sch., which is a fern (Pteridophyte) of the family Polypodiaceae.

Aspidium contains 6–15% of an oleoresin, the constituents of which include aspidinol, filicinic acid, filicic acid, albaspidin and flavaspidic acid. Aspidium also contains about 5% of a yellow amorphous acidic substance, filmarone, a fixed oil, flavaspidinol (about 6%), filicitannic acid (7–8%), filicin, a lactone of filicic acid, flavaspidic acid, resin, and starch. Aspidium is a strong anthelmintic drug, and it is used to kill and expel intestinal worms including tapeworms.

Podophyllum: Podophyllum Rhizome, Podophylli Rhizoma, Mayapple Root, American Mandrake; Podophyllum consists of the dried rhizome of Podophyllum peltatum Linn., a low-growing woodland plant of the family Berberidaceae.

The chief chemical constituent of Podophyllum is a crystalline substance, called podophyllotoxin, and a resin, podo phylloresin (podophyllin). It also contains quercetin and a large amount of starch. Podophyllum acts as a gastrointestinal irritant. In moderate doses, it is used as a drastic purgative in the treatment of constipation, caused due to hepatic troubles. A podophyllin paint of podophyllum is used in the treatment of warts.

Rhubarb-Rheum, Rhei Rhizoma, Rhei Radix, Rhubarb Rhizome; Rhubarb consists of the dried peeled rhizome of various Rheurn species, particularly Rheum palmatum Linn. and Rheum officinale Baillon, but not of Rheum rhaponticum Linn. These plants belong to the family Polygonaceae.

Rhubarb mainly contains 2.0–4.5% of anthraquinone glycosides, which include aloe-emodin, chrysophanol, physcion, rhein, and their derivatives. In addition to these glycosides, Rhubarb also contains glucogallin, gallic acid, rheinotannic acid, catechin, starch, sugars, fat, pectin, and calcium oxalate. Rhubarb is used as a laxative drug. In larger doses, it causes purgation. In smaller doses, it is a bitter stomachic and intestinal astringent. It is also given in cases of indigestion with diarrhea.

Turmeric-Turmeric Rhizome, Curcumae Rhizoma; Turmeric consists of the boiled and dried whole or split and unpeeled rhizome of Curcuma domestica Val. and Curcuma longa Linn. of the family Zingiberaceae.

Turmeric contains about 6% of volatile oil, and about 5% of a crystalline yellow substance, curcumin. It also contains resin, sugars, and starch. The fresh juice of Turmeric is used internally as a blood purifier. The paste or cream of the rhizome is applied externally for brightening skin color. The hot paste of the rhizome is used as a poultice in the treatment of inflammations and joint pains. Turmeric is also used as a coloring and dyeing agent. It is commonly used as a condiment, particularly in the Asian and African countries.

6.5.8.3 Corm

Corms are condensed forms of rhizomes consisting of stout, solid fleshy underground stems growing vertically (Fig. 6.56). They are usually more or less rounded in shape or often somewhat flattened. Corms bear one or more buds in the axils of scale leaves. They produce adventitious roots on their under surface and also on their sides. Colchicum corm is a good example of corm drugs. Coichicum consists of the fresh or dried corm of *Colchicum auturnnale* of Liliaceae. The drug contains coichicine alkaloid (0.5–0.6%) and abundant starch grains. Colchicum corm is used mainly to treat acute attack of gout and certain other gouty affections. It relieves the pain and inflammation caused by gouty affections and shortens the duration of these diseases. The alkaloid colchicine is widely used in agriculture to induce polyploidy in crop plants.

Fig. 6.56 Corm of amorphophillus

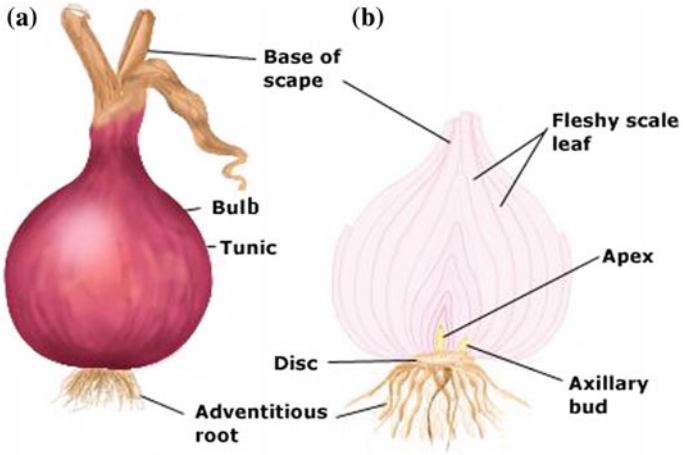


Fig. 6.59 Bulb of *Allium cepa* (**a**), the same in L.S. (**b**)

6.5.8.4 Bulb

Bulb consists of a shortened convex or slightly conical stem, a terminal bud and numerous scale leaves. The scale leaves grow from the upper surface of the stem or from around it, while a cluster of adventitious roots arise from its base. Drugs, which are represented by the fleshy scale leaves of bulbs include Squill, Garlic, and Onion (Fig. 6.57).

Squill-Scilla, Scillae Bulbus, cillae Radix; Squill consists of the sliced and dried fleshy scale leaves of the bulb of *Urginea maritima* of Liliaceae.

Squill contains a number of cardiac glycosides including scillaren A and scillaren B. It also contains flavonoids, sinistrin, mucilage (4–11%), and calcium oxalate.

Squill is a heart-muscle stimulant and a powerful expectorant. It is used to improve the tone of the heart muscle of weak hearts and in the treatment of thronic bronchitis and coughs.

6.6 Unorganized Drugs

The unorganised drugs consist of some natural substances, which are derived from plants and animals by a number of extraction processes like incision, decoction, expression, distillation and percolation or as natural secretions. Thus, these drugs are devoid of definite histological or cellular structures, that is, they are not built up into any definite plant or animal organs (acellular). They represent both physiological and pathological products of plants and animals, and occur as solids, semi-solids, and liquids depending on the type of the products constituting the drug.

The unorganized drugs may be made up of dried latex (e.g., opium, papain), dried juice (e.g., aloe, kino), dried extracts (e.g., agar, alginate, catechu, curare, pectin), gums, (e.g., acacia, guar gum, Indian gum, sterculia, tragacanth), resins, (e.g., asafetida, colophony, copaiba, guaiacum, benzoin, gamboge, myrrh), balsams, (e.g., canada balsam, tolu balsam, peru balsam, storax), fixed oils and fats (e.g., olive oil, castor oil, cotton seed oil, linseed oil), volatile oils (e.g., clove oil, cinnamon oil, lemon oil), animal products (e.g., bee wax, cantharides, cod-liver oil, gelatin, halibut liver oil, honey, shark liver oil, shellac, spermaceti wax, wool fat, musk, lactose) and fossil organism and minerals (e.g., bentonite, kaolin, kieselguhr, talc).

(i) Latex-Latices are the naturally occurring thick, sticky turbid fluids which occur as suspensions or emulsions in the laticiferous cells, laticiferous tubes, and vessels of some plants. The liquid medium of the latex suspension or emulsion consists of an aqueous solution of mineral salts, proteins, sugars, tannin, alkaloids, and other chemical substances, and the suspended particles are oil droplets, resins, gums, proteins, starch and, other similar substances The latex may be white in color, as in the Opium capsule; milky white, as in Calotropis leaf, or yellow, as in Chelidonium and Nerium species, or red, as in the rhizome of *Sanguinaria canadensis*, or colorless, as in the young fruits of *Carica papaya*. They are obtained from their natural sources by marking suitable incisions on the plant parts and evaporating the exuded latex naturally or artificially. Opium is the dried latex obtained from the mature but unripe capsules of Opium poppy, *Papaver somniferum* of Papaveraceae. Opium contains principally about 25 isoquinoline alkaloids including morphine, codeine, papaverine, thebaine, and many others. It also contains meconic acid, meconin, resin, and gum. Opium is a narcotic drug, analgesic agent to relieve

pain which is chiefly used as a strong diaphoretic analgesic agent to relieve pain. It is also used as a hypnotic drug and as a diaphoretic. Papain is the dried purified latex of the unripe fruit of *Carica papaya* of Caricaceae. Papain is a mixture of several enzymes including several proteolytic enzymes, a renin-like coagulating enzyme, an amylolytic enzyme, a clotting enzyme, and a weak fat hydrolyzing enzyme. Papain is used as a digestant for proteins and as a mucosolvent. It is extensively used as meat tenderizers.

(ii) Juices are natural aqueous fluids that drain out from cut surfaces of plant parts or are obtained by cutting plant parts into pieces, squeezing, and straining the fluid out them. Aloe consists of the evaporated juice, which drains from the cut leaves of various species of Aloe spp. of Liliaceae. According to their natural sources, the following three important commercial varieties of Aloe are derived from three different sources, e.g., Cape aloe (from *Aloe ferox*), Curacao aloe (from *Aloe vera*) and Socotrine aloe (from *Aloe perryi*). The principal constituents of Aloe are anthraquinone glycosides, e.g., barbaloin, iso-barbaloin, Beta-barbaloin, and aloe—emodin. Aloe also contains a pale yellow volatin oil and resin. Aloe is used as a cathartic drug, purgative, and as a pharmaceutic necessity in Compound Benzoin Tincture.

Extracts are usually prepared by evaporating the aqueous decoctions of various parts of certain plants. Catechu is a dried aqueous extract, prepared from the leaves and young shoots of *Uncaria gambier* of Rubiaceae and also from *Acacia catechu* of Fabaceae by boiling the wood in water and evaporating the resulting brew. Catechu contains 7–33% of catechin, 22–50% of catechutannic acid, and small quantities of catechu—red, quercetin, and gambier fluorescin. Catechu is medicinally used as a local or general astringent drug. It is very commonly eaten in Asian countries along with betel leaf for its soothing effects. Agar is the bleached and dried gelatinous substance obtained by concentrating a decoction made from various species of Gelidium and Gracilaria and other closely allied red algal seaweeds of Rhodophyceae. The chief constituent of agar is gelose, a calcium salt of the sulfuric ester of a carbohydrate complex. The medicinal value of agar is in its absorptive and lubricating action. In pharmacy, it is used as a suspending agent and a bulk laxative.

(iii) Gums are some abnormal pathological products produced by plants usually as a protective after injury or under certain unfavorable conditions of growth. They are usually produced by the dissolution or conversion of the cell walls of tissues to form sticky thick fluids, which on exudation or exposure to atmosphere solidify and turn to amorphous, translucent solid, soluble in water and yield viscous, adhesive solutions or swell up in a jelly like mass by absorbing moisture. Chemically, they are composed of calcium, potassium, and magnesium salts of polyuronides. On boiling with dilute acids, they yield mixtures of sugars and organic acids. Gums are used in pharmacy as adhesives, binders and as emulsifying and suspending agents. Acacia gum consists of the dried gummy exudate from the stems and branches of *Acacia senegal* and other

related African species of Acacia of Fabaceae. The principal constituent of Acacia is arabin, a complex mixture of calcium, potassium, and magnesium salts of arabic acid. On hydrolysis, it yields L arabnose, L-rhamnose galactose, and glucuronic units. Acacia is used as a suspending agent, a demulcent and in tablet granulation. It is a gum of choice for pharmaceutical preparations. Tragacanth is the dried gummy exudate obtained by incision from the stems of *Astragalus gumrnifer* and some other species of Astragalus of Fabaceae. Tragacanth contains a water-soluble tragacanthin, a water insoluble basorin, traces of starch, cellulose and nitrogenous substances. Tragacanth is principally used as a binder in tablets and a suspending agent in mixtures. It is also used as a thickening agent in calico printing.

(iv) Resins occur in special ducts or cavities in plant tissues. When dry they are usually hard, transparent, or translucent amorphous solids, which readily fuse upon heating. Chemically, they are complex mixtures of acids, alcohols, and esters. In the plant tissue, resins occur in more or less homogenous mixtures with volatile oils (oleoresins), gums (gum resins), and both gum and volatile oils (oleogum-resins). They are of considerable pharmaceutical and therapeutic importance. Colophony is a solid resin prepared by distilling off the volatile oil from the oleoresin obtained from various species of *Pinus* of Pinaceae. It contains 90% resin acids (e.g., abietic acid), resene, volatile oil, and a bitter principle. Colophony is used chiefly as an ingredient of ointments and plasters. It is principally used in veterinary medicine as and effective diuretic agent. Myrrh consists of the oleogum-resin obtained from the stem of *Commiphora molmol* and other species of Cornrniphora of Burseraceae. Myrrh contains a mixture of 2.5–8.0% of volatile oil, 57–61% of gum and 25–35% of resin. Myrrh possesses stimulant and antiseptic properties. It is used as an astringent in mouth-wash preparations. Myrrh also possesses stomächic properties.

(v) Balsams ate mixtures of some resins and resinous substances. Physical and chemical characteristics of balsams are very much similar to those of most resins and resin mixtures. The principal difference is that they contain larger proportions of cinnamic or benzoic acid or both of them or esters of these two acids. Peru balsam is the viscid fluid exuded from the trunk of *Myroxylon pereirae* of Fabaceae after the bark is beaten and scorched. Peru balsam contains a mixture of resin, benzyl benzoate, benzyl cinnamate, cinnamyl cinnamate, peruviol, vanillin, and cinnamic acid. Peru balsam is a local irritant and antiseptic. It is applied externally in certain irritating skin diseases. It is also used as a stimulating expectorant. Storax is the purified balsam obtained from the wounded trunk of *Liquidambar orientalis* of Altingiaceae. Storax contains resin, cinnamic acid, esters of cinnamic acid, vanillin, and styrene. Storax is a stimulant and antiseptic. Its uses are similar to those of Peru balsam.

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Chapter 7
Pharmacopoeia and Herbal Monograph, the Aim and Use of WHO's Herbal Monograph, WHO's Guide Lines for Herbal Monograph, Pharmacognostical Research and Monographs of Organized, Unorganized Drugs and Drugs from Animal Sources

Abstract Pharmacopoeia is a reference book for the preparation of quality medicines published by the authority of a government or a concerned society (e.g., British pharmacopoeia, Indian pharmacopoeia, Japanese pharmacopoeia), while herbal pharmacopoeia and therapeutic compendium represent qualitative and therapeutic monographs on botanicals (description of preparation on single topic). A pharmacopoeial monograph is a compiled data about Active Pharmaceutical Ingredients (API) or Products (APP) with its identification tests, assay method, impurity profile, test for impurity, solubility, etc. An herbal monograph is a document that defines a botanical drug and provides information that allows for its proper identification. It contains the basic description including nomenclature, part used, constituents, range of application, contraindications and side effects, incompatibilities with other medications, dosage, use, and action of the herb. Pharmacopoeia is an essential reference for all individuals and organizations working within pharmaceutical research and development, manufacture and testing around the globe. Herbal pharmacopoeia intends to promote the responsible use of herbal medicines with the highest possible degree of efficacy and safety through the development of standards of identity, purity, and analysis for botanicals including the review of traditional and scientific data regarding their efficacy and safety. The American Herbal Pharmacopoeia (AHP) and those of other nations (e.g., the British pharmacopoeia, the European pharmacopoeia, the pharmacopoeia of the People's Republic of China, the Indian Ayurvedic pharmacopoeia) intend to promote the responsible use of herbal medicines with the highest possible degree of efficacy and safety and disseminate such information through monographs and other publications. BP is now used in over 100 countries as an essential reference; the American Herbal Pharmacopoeia (AHP) intends to produce 300 monographs on botanicals including many of the Ayurvedic, Chinese, and Western herbs most frequently used

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in the USA; pharmacopoeia of the People's Republic of China (PPRC, Eng. ed. 2000) contains monographs for hundreds of medicinal plants used in Traditional Chinese Medicine; the Indian Herbal Pharmacopoeia (IHP) in its new edition covers 52 monographs on Indian medicinal plants; and the African Herbal Pharmacopoeia (AfrHP) provides comprehensive and up to date botanical, commercial, and phytochemical information on over fifty of the most important African medicinal plants. Many member states of WHO do not possess their own pharmacopoeia, but they follow one or more pharmacopoeia of other nations (e.g., in Australia, herbal raw materials are required to be authenticated to the relevant possible monograph in the British pharmacopoeia). Since 1999, the World Health Organization (WHO) has published 117 herbal monographs in four volumes and also an additional volume (30 monographs, 13 new and 17 adopted from the existing monographs) for the Newly Independent States (NIS) and Countries of Central and Eastern Europe (CCEE) to promote international harmony in the quality control and use of herbal medicines and to serve as models for the development of national formularies. Each of the WHO monographs contains a systematically narrated body of information of about a particular medicinal plant or crude drug on 19 points from (i) Definition, (ii) Synonym to …, (xvii) Dosage forms, (xviii) Posology, and (xix) References. This guideline for herbal monograph contains comprehensive scientific references on quality, safety, and efficacy of medicinal plants, and herbal pharmacopoeia represents qualitative and therapeutic monographs on botanicals. The monographs of WHO, however, should not be regarded as official pharmacopoeial monograph to replace official compendia. Monographs of organized drugs include crude materials of plant and animal origin such as leaves, flowers, fruit, seeds, stems, wood, bark, roots, rhizomes, ergot, ephedra or other parts, and Spanish fly, which may be entire, fragmented, or powdered, while monographs of unorganized drugs include such material as juices, gums, fixed oils, essential oils, latex, resins, fish liver oils, musk, bees' wax, certain hormones, enzymes, and antitoxins in fresh or dry states.

Keywords Pharmacopoeia · Monograph · WHO guidelines · Drug quality assurance

7.1 Pharmacopoeia Herbal Monograph

Pharmacopoeia (G: pharmako-drug, poi-make, ia-ing = drug-mak-ing, or drug-making) is a book containing directions for the identification of samples and the preparation of compound medicines, and published by the authority of a government or a medical or pharmaceutical society, e.g., British, European pharmacopoeia, Indian pharmacopoeia, US pharmacopoeia, pharmacopoeia of the People's Republic of China, Japanese pharmacopoeia, and the International pharmacopoeia. The British Pharmacopoeia (BP 2013) is the leading collection of standards for UK medicinal products and pharmaceutical substances. Produced by the British

pharmacopoeia Commission Secretariat of the Medicines and Healthcare Products Regulatory Agency, the BP makes an important contribution to public health by setting publicly available standards for the quality of medicines. Now used in over 100 countries, the BP remains an essential reference for all individuals and organizations working within pharmaceutical research and development, manufacture and testing around the globe. In a broader sense, pharmacopoeia is a reference work for pharmaceutical drug specifications. Descriptions of preparations are called monographs.

A monograph is a paper on a single topic. An herbal monograph gives a basic description of the herb used for therapeutic purpose, and it includes nomenclature, part used, constituents, range of application, contraindications, and side effects, incompatibilities with other medications, dosage, use, and action of the herb. Herbal pharmacopoeia represents qualitative and therapeutic monographs on botanicals. The pharmacopoeia contains specific monographs governing the quality of specific herbal products. The herbal monograph represents the most comprehensive and critically reviewed body of information on herbal medicine.

During the period 1999–2009, WHO published about 116 monographs on crude organized (e.g., whole plant, their parts) and unorganized drugs (e.g., oil, latex, juice, secretions). These include Herba (herb), Folium (leaf), Bulbus (bulb), Radix (root), Flos (flower), Fructus (fruit), Cortex (bark), Rhizoma (rhizome), or Olium (oil). Recently, the American Botanical Council has published four books of monographs such as the Complete German Commission E Monographs, Herbal Medicine: Expanded Commission E Monographs, the ABC Clinical Guide to Herbs, and the Identification of Medicinal Plants. A European Union (EU) herbal monograph (the Community herbal monograph of the past) contains the scientific opinion on safety and efficacy data about a herbal substance and its preparations intended for the medicinal use of the Committee on Herbal Medicinal Products (HMPC). The HMPC evaluates all available information, including non-clinical and clinical data, but also documented long-standing use and experience in the EU. EU monographs provide all information necessary for the use of a medicinal product containing a specific herbal substance or preparation and form the basis for the required individual medicinal product information. EU monographs are divided into two sections such as well-established use (marketing authorization) demonstrated with sufficient safety and efficacy data and traditional use (simplified registration) accepted on the basis of sufficient safety data and plausible efficacy.

7.2 The Aim and Use of WHO's Herbal Monograph

The herbal monograph provides (i) scientific information on the safety, efficacy, and quality control/quality assurance of widely used medicinal plants, in order to facilitate their appropriate use in member states; (ii) models to assist member states in developing their own monographs or formularies for these or other herbal medicines; and (iii) facilitate information exchange among member states.

The WHO through its publication (4 + 1 volumes) and other activities encourages member countries to provide safe and effective traditional remedies and practices in public and private health services. WHO's monographs, however, are not pharmacopoeial monographs, and they are not intended to replace official compendia (e.g., pharmacopoeias, formularies, or legislative documents). The monographs are intended primarily to promote harmonization in the use of herbal medicines with respect to levels of safety, efficacy, and quality control. These aspects of herbal medicines depend greatly on how the individual dosage form is prepared. For this reason, local regulatory authorities, experts, and health workers, as well as the scientific literature, should be consulted to determine whether a specific herbal preparation is appropriate for use in primary health care.

Since 1999, WHO has published 116 monographs on selected medicinal plants in 1–4 volumes of monographs: Volume 1 contains 28 monographs, volume 2 includes 30 monographs, volume 3 includes 31 monographs, and volume 4 includes 28 monographs. These four volumes of monographs were published in 1999, 2003, 2007, and 2009, respectively. Crude organized and unorganized drugs obtained from whole plant and their parts, e.g., root, shoot, leaf, flower, fruit, seeds, bark, wood, bulb, corm, rhizome, oil, latex, juice, and secretions, were named as Herba (herb), Folium (leaf), Bulbus (bulb), Radix (root), Flos (flower), Fructus (fruit), Cortex (bark), Rhizoma (rhizome), and Olium (oil) in 1–4 volumes of WHO's monographs.

Volume 1 contains monographs of Bulbus Allii Cepae, Bulbus Allii Sativi, Aloe, Aloe Vera Gel, Radix Astragali, Fructus Bruceae, Radix Bupleuri, Herba Centellae, Flos Chamomillae, Cortex Cinnamomi, Rhizoma Coptidis, Rhizoma Curcumae Longae, Radix Echinaceae, Herba Echinaceae Purpureae, Herba Ephedrae, Folium Ginkgo, Radix Ginseng, Radix Glycyrrhizae, Radix Paeoniae, Semen Plantaginis, Radix Platycodi, Radix Rauwolfiae, Rhizoma Rhei, Folium Sennae, Fructus Sennae, Herba Thymi, Radix Valerianae, and Rhizoma Zingiberis.

Volume 2 contains monographs of Radix Althaeae, Herba Andrographidis, Radix Angelicae Sinensis, Flos Calendulae, Flos Caryophylli, Rhizoma Cimicifugae, Folium cum Flore Crataegi, Radix Eleutherococci, Aetheroleum Eucalypti, Folium Eucalypti, Cortex Frangulae, Folium et Cortex Hamamelidis, Semen Hippocastani, Herba Hyperici, Aetheroleum Melaleucae, Folium Melissae, Aetheroleum Menthae Piperitae, Folium Menthae Piperitae, Folium Ocimi sancti, Oleum Oenotherae Biennis, Rhizoma Piperis Methystici, Cortex Pruni Africaniae, Cortex Rhamni Purshianiae, Flos Sambuci, Radix senegae, Fructus serenoae Repentis, Fructus silybi Mariae, Herba Tanaceti Parthenii, Radix Urticae, and Folium Uvae Ursi.

In volume 3, Fructus Ammi Majoris, Fructus Ammi Visnagae, Fructus Anethi, Aetheroleum Anisi, Fructus Anisi, Semen Armenicae, Flos Arnicae, Folium Azadirachti, Oleum Azadirachti, Flos Carthami, Stigma Croci, Fructus Foeniculi, Radix Gentianae Luteae, Radix Gentianae Scabrae, Gummi Gugguli, Radix Harpagophyti, Rhizoma Hydrastis, Radix Ipecacuanhae, Aetheroleum Lavandulae, Flos Lavandulae, Strobilus Lupuli, Gummi Myrrha, Herba Passiflorae, Testa Plantiginis, Radix Rehmanniae, Fructus Schisandrae, Radix Scutellariae, Radix

cum Herba Taraxaci, Semen, Trigonellae Foenugraeci, Cortex Uncariae, and Fructus Zizyphi are included.

Volume 4 contains descriptions on Fructus Agni Casti, Cortex Berberidis, Gummi Boswellii, Semen Cardamomi, Fructus Chebulae, Semen Cucurbitae, Folium Cynarae, Cortex Granati, Pericarpium Granati, Folium Guavae, Lichen Islandicus, Fructus Macrocarponii, Cortex Magnoliae, Herba Millefolii, Fructus Momordicae, Fructus Myrtilli, Radix Panacis Quinquefolii, Cortex Phellodendron, Rhizoma Picrorhizae, Oleum Ricini, Aetheroleum Rosmarini, Folium Rosmarini, Cortex Salicis, Fructus Tribuli, Flos Trifolii, Ramulus cum Uncis Uncariae, Cortex Viburni Prunifolii, and Radix Withaniae.

In addition to these, to meet demands of Newly Independent States (NIS) and Countries of Central and Eastern Europe (CCEE) and to regulate herbal medicines and ensure their safety, efficacy, and quality of these countries, WHO has provided technical guidance and worked with the national health authorities of interested NIS and CCEE to develop their own subregional monographs on commonly used medicinal plants. WHO monographs on medicinal plants commonly used in the Newly Independent States (NIS) include Bulbus Allii Sativi, Radix Althaeae, Herba Bidentis, Flos Calendulae, Flos Chamomillae, Herba Chelidonii, Folium cum Flore Crataegi, Herba Equiseti, Fructus Foeniculi, Radix Ginseng, Radix Glycyrrhizae, Flos Helichrysi arenarii, Fructus Hippophaës recens, Herba Hyperici, Herba Leonuri, Folium Melissae, Aetheroleum Menthae Piperitae, Folium Menthae Piperitae, Herba Millefolii, Herba Origani, Herba Pegani harmalae, Folium Plantaginis majoris, Herba Polygoni avicularis, Folium Salviae, Folium Sennae, Radix cum Herba Taraxaci, Herba Thymi, Flos Tiliae, Radix Urticae, and Styli cum stigmatis Zeae maydis (WHO 2006). This NIS publication includes 30 monographs: 13 were new monographs to address unique medicinal plants commonly used in the NIS, and 17 were adopted from the existing four volumes of WHO monographs on selected medicinal plants that were identified as the most widely or commonly used in the NIS.

The monographs are intended to promote international harmonization in the quality control and use of herbal medicines and to serve as models for the development of national formularies. They are a comprehensive scientific reference for drug regulatory authorities, physicians, traditional practitioners, pharmacists, manufacturers, and research scientists. The WHO's monographs on selected medicinal plants aim to provide scientific information on the safety, efficacy, and quality control of widely used medicinal plants; provide models to assist member states in developing their own monographs or formularies; and facilitate information exchange among member states. Each monograph follows a standard format with information presented in two parts followed by a reference list. The first part presents pharmacopoeial summaries for quality assurance. The second part includes sections on medicinal uses, pharmacology, safety issues, and dosage forms. The descriptions under the medicinal uses section merely represent the systematic collection of scientific information available at the time of each volume's preparation and should not be taken as having WHO's official endorsement or approval.

The monographs are not only a valuable scientific reference for health authorities, scientists, and pharmacists, but will also be of interest to the general public. WHO's monographs will continue to play an important role in promoting the proper use of medicinal plants throughout the world. WHO's monographs, however, are not intended to be official pharmacopoeia monograph where pharmacopoeia monograph is a compiled data about Active Pharmaceutical Ingredients (API) or Product (APP) with its identification tests, assay method, impurity profile, test for impurity, solubility, etc. Moreover, this publication is not intended to replace official compendia (e.g., pharmacopoeia, formularies, or legislative documents). Furthermore, the descriptions included in the section on medicinal uses merely represent the systematic collection of scientific information available at the time of preparation, for the purpose of facilitating information exchange.

7.3 WHO's Guidelines for Herbal Monograph

According to WHO format, monograph of a medicinal plant (or crude drug) contains available information in two parts, followed by a reference list: One part contains pharmacopoeial summaries for quality assurance, and another part contains information on medicinal uses, pharmacology, safety issues, and dosage forms. For herbal monograph, a medicinal plant is generally described on different heads such as (i) Definition; (ii) Synonym; (iii) Selected vernacular names; (iv) Geographical distribution; (v) Description; (vi) Plant material of interest (e.g., dried shoot, leaf, bud, flower, fruit, seed, and powdered plant material; their general appearance, organoleptic properties, microscopic characteristics, and others); (vii) General identity tests; (viii) Purity tests (e.g., microbiology, foreign organic matter, total ash, acid-insoluble ash, water-soluble extractive, loss on drying, swelling index, pesticide residues, heavy metals, radioactive residues, other purity tests); (ix) Chemical assays; (x) Major chemical constituents; (xi) Medicinal uses (e.g., uses supported by clinical data, uses described in pharmacopoeias and in traditional systems of medicine, uses described in folk medicine, not supported by experimental or clinical data); (xii) Pharmacology (e.g., experimental pharmacology, anti-inflammatory activity, antitussive activity, clinical pharmacology); (xiii) Contraindications; (xiv) Warnings; (xv) Precautions (e.g., drug interactions, other precautions); (xvi) Adverse reactions; (xvii) Dosage forms; (xviii) Posology; and (xix) References.

Definition describes the identity of the plant material of interest and the Latin binomial name of the source plant, the binomial name being the most important criterion in quality assurance of the crude drug. Latin pharmacopoeial synonyms and vernacular names are listed in the sections. Synonyms and Selected vernacular names, respectively, are those names used in commerce or by local consumers. The monographs place outdated botanical nomenclature in the synonyms category, based on the International rules of nomenclature. The vernacular names listed are a selection of names from individual countries worldwide, in particular from areas

where the medicinal plant is in common use. Geographical distribution is not normally found in official compendia, but it is included in monograph to provide additional quality assurance information. In Description, a detailed botanical description is intended for quality assurance at the stages of production and collection of the source plant, whereas the detailed description of the specific plant part used (the crude drug like leaf, stem, wood, bark, flower, fruit, seed, etc.), in Plant material of interest, is for quality assurance at the manufacturing and commercial stages. General identity tests, Purity tests, and Chemical assays are all normal compendial components included under those headings in the monograph. Where purity tests do not specify accepted limits, those limits should be set in accordance with the requirements of the respective national health authorities. Each medicinal plant and crude drug contains active or major chemical constituents with a characteristic profile that can be used for chemical quality control and quality assurance. These constituents are described in the section of Major chemical constituents. Medicinal uses include uses supported by clinical data; uses described in pharmacopoeias and in traditional systems of medicine; and uses described in folk medicine, not yet supported by experimental or clinical data. The first category includes medicinal indications that are well established in some countries and have been validated by clinical studies documented in the scientific literature. The clinical trials include controlled, randomized, double-blind studies, trials without controls, cohort studies, or well-documented observations of therapeutic applications. The second category includes medicinal uses that are well established in many countries and are included in official pharmacopoeias or national monographs. The Experimental pharmacology section includes only the results of investigations that prove or disprove the cited medicinal uses. The references cited provide additional information useful in evaluating specific herbal preparations.

7.4 Pharmacognostical Research and Development of Herbal Monograph in Different Countries

The use of medicinal plants is widespread and supported by public policies in many developing and developed countries, mostly as non-prescription drugs. These herbal drugs are used for primary health care purposes in developing and maintaining popularity because of historical and cultural reasons. In spite of the availability of modern medicine, they are also gaining popularity in alternative or complementary therapies in many developed countries. Assurance of the safety, quality, and efficacy of medicinal plants and herbal products has now become a key issue in industrialized and in developing countries. Pharmacognostical research and development of herbal monographs are prerequisite for safe, effective, and quality herbal medicine. For the development of safe and quality products, herbal monographs usually contain all available information of the herb including scientific names, synonyms, vernacular names, parts of the herb used, geographical

distribution, macroscopic and microscopic examination for authenticity and purity, chemical test for active principles, dosage forms, medicinal uses, pharmacology, drug interactions, etc., as suggested by the World Health Organization (1999). Monographs are included in pharmacopoeia of many countries such as the International pharmacopoeia, the US Pharmacopoeia (USP) and the USP National Formulary, the European pharmacopoeia (created in 1964, contains 83 monographs), and pharmacopoeia of India, German, French, Portuguese, Africa, China, Dutch, Argentinean, British, European, French, Japan, Mexico, Hungary, Portuguese, and also in other publications (book, journal, data base, etc.). Like the WHO, monographs on selected medicinal plants are also available from the European Scientific Cooperative on Phytotherapy (ESCOP) and German Commission E (Bluementhal et al. 1998; ESCOP 1999; WHO 1999). Natural Medicines Comprehensive Database, NAPRALERT, database published by Bhat, etc., are some other resources information about herbal products (Bhat 1995; Natural Products ALERT 2001; Jellin 2002).

The worldwide spread in the use of herbal medicines has produced various attempts to develop herbal monographs to define identity and quality criteria. However, the monographs developed and published in different countries do not conform to the international standards, especially those of European Scientific Cooperative on Phytotherapy (ESCOP) (Awang 1997) or those of the World Health Organization (1997). WHO developed 116 monographs of selected medicinal plants following the guidelines for the assessment of herbal medicines adopted by the International Conference of Drug Regulatory Authorities (ICDRA). They do not present unified information regarding medicinal plants (about botany, agronomy, quality control, safety, and efficacy and also about relating regulatory aspects that support herbal medicine regulation and do not cover enough requirements for herbal medicine registration). Under the circumstances, a monograph template is necessary to systematize the available information on medicinal plants of interest including general information, botanical authentication, pharmacognostic authentication cultivation, agronomical information, quality control, safety and efficacy, market, regulatory issues, and references. The monographs need to be supplemented and updated periodically on the basis of the appearance of new information in the different literature on safety, quality, and efficacy herbal products, and likewise, additional monographs may be prepared. More research activities are necessary to develop comprehensive informative monographs for use as sources of information of medicinal plants including quality control tests for synthetics and herbal medicines, safety of herbal formulations for pharmaceutical compounding.

7.5 Monographs of Organized and Unorganized Drugs

Monograph is a paper on a single topic, and herbal monographs normally include information on nomenclature, part used, constituents, range of application, contraindications, side effects, incompatibilities, dosage, use, action of the herb, etc.

Monographs of some organized drugs consisting of whole plant or herb, leaf, bark, and root, e.g., (i) Herba Centellae, (ii) Folium Ocimi Sancti, (iii) Folium Sennae, (iv) Bulbus Allii Sativi, (v) Cortex Cinnamomi, (vi) Radix Rauwolfiae, (vii) Rhizoma Curcumae Longae, and (viii) Rhizoma Zingiberis as well as unorganized drugs consisting of latex, juice, and oils, e.g., (ix) Aloe, (x) Aloe Vera Gel, and (xi) Oleum Azadirachti are described below following the publication of the World Health Organization (WHO) on selected medicinal plants (vol. 1–3). In addition to these, some organized (e.g., Hirudina medicinalis, Cantharides) and unorganized drugs (e.g., cod-liver oil, halibut-liver oil, suet, lard, spermaceti, gelatin, honey, waxes) from animal sources are described in the form of monograph.

7.6 Monographs of Organized Drugs

7.6.1 Herba Centellae

Definition: Herba Centellae consists of the dried aerial parts or the entire plant of *Centella asiatica* (L.) Urban. (Apiaceae) (1–5).

Synonyms: *Centella coriacea* Nannfd., *Hydrocotyle asiatica* L., *Hydrocotyle lunata* Lam., and *Trisanthus cochinchinensis* Lour. (1, 3, 6). Apiaceae are also known as Umbelliferae.

Selected vernacular names: Asiatic pennywort, Indian pennywort, water pennywort, waternavel (3–11).

Description: A slender trailing herb, rooting at the nodes. Leaves 1.3–6.3 cm diameter, orbicular reniform, more or less cupped, entire, crenate or lobulate, glabrous; leaf stalks 2–5 cm long; peduncle about 6 mm, often 2–3 nates; pedicels nil; bracts small, embracing the flowers; inflorescence in single umbel, bearing 1–5 flowers, sessile, white or reddish; fruit small, compressed, 8 mm long, mericarps longer than broad, curved, rounded at top, 7–9-ridged, secondary ridges as prominent as the primary, reticulate between them; pericarp much thickened; seed compressed laterally (1, 4, 7).

Plant material of interest: aerial part or entire plant

General appearance: A slender herb. Stems long, prostrate, emerging from the leaf-axils of a vertical rootstock, filiform, often reddish, with long internodes and rooting at the nodes; leaves thin, long-petioled, several from the rootstock and 1–3 from each node of the stems, 1.3–6.3 cm diameter, orbicular reniform, more or less cupped, entire, crenate or lobulate, glabrous; petioles very variable in length, 7.5–15 cm long or more, channelled; stipules short, adnate to the petioles forming a sheathing base (4, 5).

Organoleptic properties: Color, grayish green; odor, characteristic; taste, slightly bittersweet (4, 5).

Microscopic characteristics: Grayish green with stomata on both surfaces of the leaf, 30 by 28 μm, mostly rubiaceous type. Palisade cells differentiated into two layers of cells, 45 by 25 μm; spongy parenchyma of about three layers of cells with many intercellular spaces, some with crystals of calcium oxalate; midrib region shows two or three layers of parenchymatous cells without chloroplastids; petiole shows epidermis with thickened inner walls; collenchyma of two or three layers of cells; a broad zone of parenchyma; seven vascular bundles within parenchymatous zone, two in projecting arms and five forming the central strand; vessels 15–23 μm in diameter. Some parenchymatous cells contain crystals of calcium oxalate. Fruits, epidermis of polygonal cells, trichomes similar to the leaves, sheets of elongated parquetry layer cells, bundles of narrow annular vessels, and parenchymatous cells contain single large prisms of calcium oxalate (4).

Geographical distribution: The plant is indigenous to the warmer regions of both hemispheres, including Africa, Australia, Cambodia, Central America, China, Indonesia, the Laos People's Democratic Republic, Madagascar, the Pacific Islands, South America, Thailand, southern USA, and Vietnam. It is especially abundant in the swampy areas of India, the Islamic Republic of Iran, Pakistan, and Sri Lanka up to an altitude of approximately 700 m (1, 4, 6, 8, 10, 11).

General identity tests: Macroscopic and microscopic examinations; microchemical tests for the presence of triterpenes and reducing sugars (1, 4).

Purity tests

Microbiology: The test for *Salmonella* spp. in Herba Centellae products should be negative. The maximum acceptable limits of other microorganisms are as follows (12–14). For the preparation of decoction: aerobic bacteria, not more than 10^7/g; fungi, not more than 10^5/g; *Escherichia coli,* not more than 10^2/g. Preparations for internal use: aerobic bacteria, not more than 10^5/g or ml; fungi, not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria, not more than 10^3/g or ml; *Escherichia coli,* 0/g or ml.

Foreign organic matter: Not more than 2% (4).

Total ash: Not more than 19% (2, 3).

Acid-insoluble ash: Not less than 6% (2).

Water-soluble extractive: Not less than 6% (2, 3).

Alcohol-soluble extractive: Not less than 9.5% (2, 3).

Pesticide residues: To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Herba Centellae is not more than 0.05 mg/kg (14). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (12) and guidelines for predicting dietary intake of pesticide residues (15).

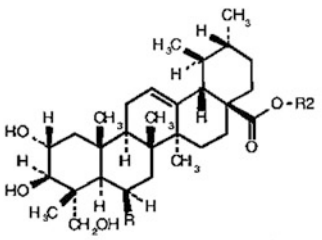
Heavy metals: Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (12).

Radioactive residues: For analysis of strontium-90, iodine-131, cesium-134, cesium-137, and plutonium-239 (12).

Other purity tests: Chemical tests and tests for drug interactions and moisture to be established by national authorities.

Chemical assays: Contains not less than 2% triterpene ester glycosides (asiaticoside and madecassoside) (10). Determination of asiaticoside and related triterpene ester glycosides by thin-layer chromatography (16) and spectroscopic analysis (17).

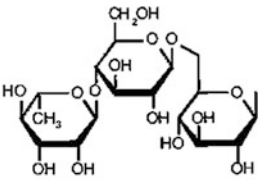
Major chemical constituents: The major principles in Herba Centellae are the triterpenes asiatic acid and madecassic acid, and their derived triterpene ester glycosides, asiaticoside and madecassoside (8, 10, 11).



asiatic acid R1 = H , R2 = OH
madecassic acid R1 = OH , R2 = OH

rha-glc-glc- =

O-α-L-rhamnopyranosyl-(1→4)-*O*β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl
or
O-6-deoxy-α-L-mannopyranosyl-(1→4)-*O*-β-D-glucopyranosyl-(1→6)-β-D-glucopyranosyl



asiaticoside R1 = H , R2 = rha-glc-glc-
madecassoside R1 = OH , R2 = rha-glc-glc-

Dosage forms: Dried drug for infusion (18); galenic preparations for oral administration (10). Powder or extract (liquid or ointment) for topical application (1, 4). Package in well-closed, light-resistant containers.

Medicinal uses

Uses supported by clinical data: Treatment of wounds, burns, and ulcerous skin ailments and prevention of keloid and hypertrophic scars (10, 18–21). Extracts of the plant have been employed to treat second- and third-degree burns (19). Extracts have been used topically to accelerate healing, particularly in cases of chronic postsurgical and post-trauma wounds (19). Extracts have been administered orally to treat stress-induced stomach and duodenal ulcers (10).

Uses described in pharmacopoeias and in traditional systems of medicine: Herba Centellae is reported to be used in the treatment of leprous ulcers and venous disorders (5, 6, 8, 10, 22).

Studies suggest that extracts of *Centella asiatica* cause regression of inflammatory infiltration of the liver in cirrhosis patients (10, 23). Further experimentation is needed to confirm these findings.

Uses described in folk medicine, not supported by experimental or clinical data: Therapy of albinism, anemia, asthma, bronchitis, cellulite, cholera, measles, constipation, dermatitis, diarrhea, dizziness, dysentery, dysmenorrhea, dysuria, epistaxis, epilepsy, hematemesis, hemorrhoids, hepatitis, hypertension, jaundice, leukorrhea, nephritis, nervous disorders, neuralgia, rheumatism, smallpox, syphilis,

toothache, urethritis, and varices; as an antipyretic, analgesic, anti-inflammatory, and 'brain tonic' agent (*4*, *5*, *7*). Poultices have been used to treat contusions, closed fractures, sprains, and furunculosis (*7*).

Pharmacology

Experimental pharmacology: The pharmacological activity of *Centella asiatica* is thought to be due to several saponin constituents, including asiaticoside, asiatic acid, and madecassic acid (*10*). In vitro, each of these compounds stimulated the production of human collagen I, a protein involved in wound healing (*24*). Stimulation of collagen synthesis in foreskin fibroblast monolayer cultures by an extract from Herba Centellae has also been reported (*25*). Asiaticoside accelerated the healing of superficial postsurgical wounds and ulcers by accelerating cicatricial action (*21*). Asiaticoside stimulates the epidermis by activating the cells of the malpighian layer in porcine skin and by keratinization in vitro (*26*). Topical application of asiaticoside promoted wound healing in rats and significantly increased the tensile strength of newly formed skin (*21*, *27*).

Extracts of *C. asiatica*, and in particular its major triterpene ester glycoside, asiaticoside, are valuable in the treatment of hypertrophic scars and keloids (*21*). Asiaticoside has been reported to decrease fibrosis in wounds, thus preventing new scar formation (*21*). The mechanism of action appears to be twofold: by increasing the synthesis of collagen and acidic mucopolysaccharides, and by inhibiting the inflammatory phase of hypertrophic scars and keloids. It has further been proposed that asiaticoside interferes with scar formation by increasing the activity of myofibroblasts and immature collagen (*21*).

Extract of Herba Centellae effectively treated stress-induced stomach and duodenal ulcers in humans (*10*, *28*). Oral administration of *C. asiatica* extract to rats produced a dose-dependent reduction in stress-induced gastric ulceration, and the antiulcer activity was similar to that of famotidine (*29*). The mechanism of action appears to be associated with a central nervous system-depressant activity of *C. asiatica*, owing to an increase in the concentration of GABA (γ-aminobutyric acid) in the brain (*29*).

A 70% ethanol extract of the drug administered intraperitoneally to mice produced anticonvulsant activity (*30*).

Clinical pharmacology: In clinical trials, an extract of *C. asiatica* in a 1% salve or 2% powder accelerated healing of wounds (*31*). A formulation containing asiaticoside as the main ingredient healed 64% of soiled wounds and chronic or recurrent atony that was resistant to usual treatment (*21*). In an open clinical study, treatment of 20 patients with soiled wounds and chronic or recurrent atony with a galenical formulation containing 89.5% *C. asiatica* healed 64% and produced improvement in another 16% of the lesions studied (*20*). Local application of an extract of the drug to second- and third-degree burns expedited healing, prevented the shrinking and swelling caused by infection, and further inhibited hypertrophic scar formation (*11*).

Twenty-two patients with chronic infected skin ulcers were treated with a cream containing a 1% extract of *C. asiatica* (*32*). After 3 weeks of treatment, 17 of the patients were completely healed and the ulcer size in the remaining five patients was decreased (*32*). Another trial using the same cream preparation demonstrated similar results (*33*). A standardized extract of Herba Centellae was reported to treat ulcus cruris (indolent leg ulcers) effectively in clinical trials (*34*, *35*). In a double-blind study, no significant effect on healing was observed in patients with ulcus cruris after oral treatment with asiaticoside (*36*).

Oral administration of *C. asiatica* or asiaticoside and potassium chloride capsules was reported to be as effective as dapsone therapy in patients with leprosy (*37*). In a controlled study of 90 patients with perforated leg lesions owing to leprosy, application of a salve of the plant produced significantly better results than a placebo (*11*, *22*, *38*).

Clinical trials of the drug have demonstrated its antiulcer activity after oral administration (*28*, *39*, *40*). Fifteen patients with peptic or duodenal ulcer were treated with a titrated extract of Herba Centellae (60.0 mg/person). Approximately 93% of the patients exhibited a definite improvement in subjective symptoms, and 73% of the ulcers were healed as measured by endoscopic and radiological observations (*28*).

Clinical studies of Herba Centellae in the treatment of various venous disorders have demonstrated a positive therapeutic effect (*11*). In patients suffering from venous insufficiency who were treated with a titrated extract of the drug, venous distension and edema improved significantly, as compared with controls (*41*).

Contraindications: Allergy to plants of the Apiaceae family.

Warnings: No information available.

Precautions

Carcinogenesis, mutagenesis, impairment of fertility: Asiaticoside has been implicated as a possible skin carcinogen in rodents after repeated topical application (*42*). Further experimentation is needed to substantiate this claim.

Other precautions: No information was available concerning drug interactions, drug and laboratory test interactions, teratogenic or non-teratogenic effects on pregnancy, nursing mothers, or pediatric use.

Adverse reactions: Allergic contact dermatitis has been associated with topical application of *C. asiatica* (*21*, *43*, *44*). However, further testing revealed that these reactions may be due to other ingredients in the preparations (*45*).

Posology: Oral dose: 0.33–0.68 g or by oral infusion of a similar amount three times daily (*4–6*).

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7.6.2 Folium Ocimi Sancti

Definition: Folium Ocimi Sancti consists of the fresh or dried leaves of *Ocimum sanctum* L. (Lamiaceae) (*1-3*).

Synonyms: *Moschosma tenuiflorum* (L.) Heynhold, *Ocimum album* Blanco, *O. anisodorum* Muell., *O. brachiatum* Hasskarl, *O. flexuosum* Blanco, *O. frutescens* Burm., *O. gratissimum* Lour., *O. inodorum* Burm., *O. monachorum* L., *O. nelsonii* Zipp ex Span., *O. tenuiflorum* L., *O. virgatum* Blanco (*4*).

Selected vernacular names: Badrooj, basilic des moines, bazsalikom levél, daun lampes, garden balsam, green tulsi, holy basil, huong nhu t¡ia, jagu lu myah, kamimebouki, kaphrao, kaprao, kemangi, kemangi laki, kra phrao, lampas, monk's basil, peihan, rayhhan, reihan, sacred basil, saling-kugon, saling-kugon ma, selaseh puteh, solasi, sulasi, sursa, tamole, thulasi, tjlsi, tulashi, tulasi, tulsi (*1*, *4–9*).

Geographical distribution: Indigenous to India and parts of north and eastern Africa, Hainan Island and Taiwan, China. It is cultivated in Southeast Asia (*6*, *8*, *10*).

Description: A herb or shrub, up to 1 m high, often much branched. Stem square, lower parts subserrate, higher parts slightly furrowed and more densely pubescent or subglabrous. Leaves simple, opposite, oblong, ovate or oval-oblong, 2.7–7.5 cm long, 1–3 cm wide, with acute top, cuneate, obtuse to rounded base, margin entire, undulate or serrate, both surfaces thinly pubescent and dotted; petiole 0.2–3.0 cm long. Calyx 0.2–0.4 cm long, with or without long or short hairs, ciliate, densely glandulose; upper lip 2.0–3.5 mm long, oval short-acuminate; lower lip 1.0–2.5 mm long, dentate, teeth linear-acuminate from an equal- or unequal-sided triangular to ovate base, two anterior teeth equalling or slightly surpassing the upper lip; fruiting calyx not completely closed by teeth. The upper part of the corolla villous and glandulose in the upper part; lobes of upper lip rounded, lobes of lower lip obtuse to rounded. Nutlets obovoid, dark brown or black, 1–2 mm long; pericarp swells into a slimy mass when moistened (*6*, *8*, *11*, *12*).

Plant material of interest: fresh or dried leaves

General appearance: Leaves green to greenish-brown, 2.5–7.5 cm long, 1–3 cm wide, oblong, ovate, or oval-oblong, with acute top, cuneate, obtuse to rounded base, pinnate veins, serrate or entire and undulate margin; thin but fleshy, both surfaces thinly pubescent; petiole cylindrical, 1–2 cm long, thinly pubescent (*1*).

Organoleptic properties: Odor: characteristic, aromatic; taste: slightly pungent (*1*, *2*).

Microscopic characteristics: Transverse section of the leaf through its midrib: upper epidermis consists of a layer of small, quadrangular transparent cells with thin walls, and thin smooth cuticle. On tangential view, these cells are polygonal with straight or wavy walls. The lower epidermis consists of a layer of small, quadrangular transparent cells with thin walls and thin smooth cuticle. Trichomes bent, consisting of 2–6 cells; glandular trichomes short, Lamiaceae type, consisting of 1 stalk cell and 2–4 cells with rounded heads. Palisade parenchyma consists of a layer of long cylindrical cells containing chlorophyll; spongy parenchyma consists of polygonal cells with thin, straight or slightly wavy side walls. Vascular bundles collateral type with collenchyma cells. Stomata diacytic, on upper and lower epidermis (*1*).

Powdered plant material: Upper epidermis with diacytic stomata, glandular trichomes, and palisade cells; lower epidermis with diacytic stomata and underlying spongy cells; 2- and 4-celled glandular trichomes; uniseriate, multicellular trichomes with collapsed cells; lignified fibers; spiral vessels; pollen grains rare; parenchyma; and collenchyma from petioles (*2*).

General identity tests: Macroscopic and microscopic examinations (*1*) and thin-layer chromatography (*2*).

Purity tests

Microbiological: Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (*13*).

Total ash: Not more than 13% (*1*).

Acid-insoluble ash: Not more than 1% (*1*).

Sulfated ash: Not more than 20% (*2*).

Water-soluble extractive: Not less than 5% (*1*).

Alcohol-soluble extractive: Not less than 5.0% (*2*).

Loss on drying: Not more than 14% (*2*).

Pesticide residues: The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*), and the WHO guidelines on quality control methods for medicinal plants (*13*) and pesticide residues (*15*).

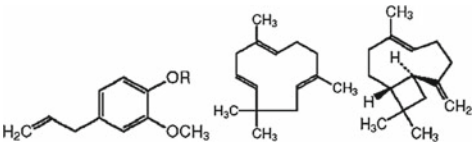
Heavy metals: For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (*13*).

Radioactive residues: Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*13*) for the analysis of radioactive isotopes.

Other purity tests: Chemical and foreign organic matter tests to be established in accordance with national requirements.

Chemical assays: Contains not less than 0.5% essential oil (*3*). Gas chromatography and gas chromatography-mass spectroscopy methods are available for qualitative and quantitative determination of volatile constituents (*16*).

Major chemical constituents: The main components are tannins (4.6%) and essential oil (up to 2%) (*1*). The amounts of the primary constituents of the essential oil vary according to the geographical distribution and variety of the source plant material: eugenol (up to 62%), methyleugenol (up to 86%), and α- and β-caryophyllene (up to 42%). Also present are methylchavicol, linalool, and 1,8-cineole (*4*, *16–19*). The structures of the major constituents are presented below.



eugenol R = H α-caryophyllene β-caryophyllene
methyleugenol R = CH_3

Medicinal uses

Uses supported by clinical data: None. Although there are some preliminary clinical data supporting the use of Folium Ocimi Sancti for the treatment of diabetes, further trials are needed to substantiate the data.

Uses described in pharmacopoeias and in traditional systems of medicine: Treatment of arthritis, asthma, bronchitis, common cold, diabetes, fever, influenza, peptic ulcer, and rheumatism (*1*, *8*, *20*).

Uses described in folk medicine, not supported by experimental or clinical data: Treatment of earache, epilepsy, heart disease, malaria, sinusitis, snake bites, stomach ache, and vomiting. Also used as an anthelminthic, to stimulate lactation, to prevent hair loss, and as a tonic (*7*).

Pharmacology—Experimental pharmacology

Analgesic activity: Intraperitoneal or intragastric administration of the fixed oil to mice (3 ml/kg body weight) significantly inhibited writhing induced by acetic acid ($P < 0.01$) (*21*). Intragastric administration of an aqueous suspension or a methanol extract of the leaves to mice (100 mg/kg body weight) showed analgesic activity in the hot-plate test (*22*).

Antispasmodic activity: A 50% ethanol extract of the leaves inhibited histamine-induced bronchospasms and pre-convulsive dyspnoea in guinea-pigs when administered by gastric lavage (200 mg/kg body weight) (*23*, *24*). Intragastric administration of the leaf essential oil or fixed oil to guinea-pigs (0.5 ml/kg body

weight) inhibited bronchospasms induced by both histamine and acetylcholine, and pre-convulsive dyspnoea (*23–25*).

A hydroalcoholic extract of the leaves inhibited muscle spasms induced by histamine in guinea-pig ileum, and muscle spasms induced by acetylcholine, barium, and histamine in guinea-pig small intestine in vitro (*26*). However, an aqueous extract showed no activity in either test system (*27*). In another study, aqueous extracts of the leaves inhibited muscle spasms induced by acetylcholine, histamine, and carbachol in rabbit intestine in vitro (*28*).

Antimicrobial activity: An ether or 95% ethanol extract of the leaves inhibited the growth in vitro of *Staphylococcus aureus* and *S. citreus* (*29*, *30*) and of *Mycobacterium tuberculosis* (*29*, *31*). A hot aqueous extract of the leaves inhibited the growth in vitro of *Trichophyton mentagrophytes* (*32*), and the growth of *Aspergillus fumigatus* and *A. niger* was inhibited in vitro when grown on agar plates containing the powdered leaves (*33*).

Anti-inflammatory activity: Intragastric administration of a hydroalcoholic extract of the leaves or the essential oil to rats and guinea-pigs (10 ml/kg body weight) inhibited footpad edema induced by histamine, serotonin, and carrageenan (*23*, *24*). Intragastric administration of the fixed oil and linolenic acid extracted from the leaf to rats inhibited footpad edema induced by prostaglandin E_2, leukotriene, carrageenan, and arachidonic acid (*34*). Intragastric administration of an aqueous leaf extract to rats (100 mg/kg body weight) inhibited footpad edema induced by croton oil and carrageenan (*22*). Intraperitoneal administration of an aqueous leaf extract to rats (100 mg/kg body weight) also inhibited carrageenan-induced footpad edema (*35*). A hydroalcoholic extract of the leaves inhibited the activity of prostaglandin synthetase by 88% in vitro at a concentration of 750 μg/ml (*36*). An aqueous leaf extract exhibited anticholinergic and antihistamine activity in guinea-pig ileum and small intestine in vitro (0.15 mg) (*27*).

Antipyretic activity: Intragastric administration of a methanol leaf extract to rats (250 mg/kg body weight) suppressed fever induced by typhoid vaccine (*35*). However, intragastric administration of a hydroalcoholic extract of the leaves to rabbits (10 mg) did not suppress fever induced by yeast (*37*).

Effect on sleeping time: Intraperitoneal administration of an aqueous or 70% ethanol extract (30–40 mg/kg body weight) of the leaves to mice potentiated sleeping time induced by hexobarbital and pentobarbital (*28*, *38*).

Immunostimulatory activity: Intragastric administration of an aqueous or methanol extract of the leaves to rats (100–500 mg/kg body weight) increased antibody titer in both sheep erythrocyte and Widal agglutination tests, thus demonstrating stimulation of the humoral immune response. The cellular immune response was also stimulated, as an increase in lymphocytosis, and E-rosette formation was also seen (*39*). Intragastric administration of a leaf essential oil to rats (100 mg/kg body weight) enhanced the titers of both anti-sheep red blood cell and IgE antibodies (*40*).

Endocrinological effects: The effects of a leaf extract on changes in serum triiodothyronine, thyroxine, and cholesterol concentrations have been investigated in mice. After 15 days of treatment (0.5 g/kg body weight, by gastric lavage),

significant decreases were observed in serum thyroxine concentration, hepatic lipid peroxidation, and hepatic glucose-6-phosphate activities. No marked change in serum triiodothyronine levels was noted. The activities of superoxide dismutase and superoxide catalase were increased (*41*).

Antiulcer activity: Intragastric administration of an ethanol extract of the leaves to rats reduced the concentration of plasma corticosterone, which had risen following 30 min of noise (100 dB), to normal levels (*42*). An organic solvent extract of the leaves had significant antioxidant activity in a variety of in vitro systems (*43*). Intragastric administration of a 70% ethanol extract of the leaves to rats (100 mg/kg body weight) prevented ulcers induced by acetylsalicylic acid and stress (*44*). Administration of the dried leaves to rats similarly prevented ulcers induced by cold and acetylsalicylic acid (*45*). However, intragastric administration of a methanol extract of dried leaves to mice (2 g/kg body weight) did not prevent stress-induced ulcers (*46*).

Hypoglycemic activity: Intragastric administration of a 50% ethanol extract of the leaves (250 mg/kg body weight) to albino rats with experimentally induced hyperglycemia reduced blood glucose levels by 30% (*26*, *47*). Intragastric administration of the leaves (50–400 mg/kg body weight) to rats with diabetes induced by streptozocin resulted in a reduction in blood glucose levels measured after fasting (*48*).

Toxicity: Intragastric administration of eugenol (400–600 mg/kg body weight) has been reported to produce liver damage in mice, whose livers were experimentally depleted of glutathione (*49*). It was also cytotoxic in isolated rat hepatocytes (*50*). However, no generalized toxicity was reported in mice after a 50% ethanol extract of the leaves was injected either intraperitoneally (1 g/kg body weight) (*26*) or intradermally (10 g/kg body weight) (*51*).

Clinical pharmacology

Asthma: In a study without controls, oral administration of an aqueous extract of dried Folium Ocimi Sancti to 20 patients with asthma increased lung vital capacity and relieved labored breathing (*52*).

Glucose and cholesterol levels: A randomized, placebo-controlled, single-blind, cross-over study assessed the effects of the dried leaves on the levels of blood glucose and serum cholesterol in 40 non-insulin-dependent diabetic patients. Patients received orally 2.5 g leaves daily for 4 weeks. Blood glucose levels, measured after fasting and eating, decreased by 17.6 and 7.3%, respectively. Mean total cholesterol level also was decreased slightly (by 6.5%) during the treatment period (*20*). No adverse effects were observed.

Contraindications: There are conflicting reports on the embryotoxicity of Folium Ocimi Sancti (*53*, *54*). The use of Folium Ocimi Sancti is therefore contraindicated during pregnancy and lactation.

Warnings: No information available.

Precautions

Drug interactions: One study has shown that eugenol may be hepatotoxic in mice with glutathione-depleted livers (*49*). Therefore, Folium Ocimi Sancti should

be used with caution in patients taking drugs such as paracetamol (acetaminophen) that deplete glutathione.

Carcinogenesis, mutagenesis, impairment of fertility: A hot aqueous extract of fresh Folium Ocimi Sancti was not mutagenic in *Bacillus subtilis* H-17 (*rec*+) and M-45(*rec*−) at a concentration of 0.5 ml/disc (*55*). Intragastric administration of the leaves prevented implantation of the embryo in various animal models (*54*, *56*). Intragastric administration of the leaves (10% of feed) to male mice inhibited spermatogenesis (*57*, *58*).

Pregnancy: teratogenic effects: There are conflicting reports on the embryotoxicity of Folium Ocimi Sancti. In one study, a benzene leaf extract was neither teratogenic nor embryotoxic when administered intragastrically to rats (200 mg/kg body weight) (*53*). However, another study demonstrated that aqueous or benzene extracts of the leaves were embryotoxic when administered intragastrically to rats (100–200 mg/kg body weight) (*54*). (See also Contraindications.)

Pregnancy: non-teratogenic effects: See Contraindications.

Nursing mothers: See Contraindications.

Other precautions: No information available on general precautions or precautions concerning drug and laboratory test interactions or pediatric use. Therefore, Folium Ocimi Sancti should not be administered to children without medical supervision.

Adverse reactions: No adverse reactions have been reported in clinical trials (*20*, *52*).

Dosage forms: Crude drug and preparations thereof (*1*).

Posology: (Unless otherwise indicated) Daily dosage: 6–12 g crude drug as a decoction (*8*).

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7.6.3 Radix Rauwolfiae

Definition: Radix Rauwolfiae is the dried root of *Rauvolfia serpentina* (L.) Benth. ex Kurz (Apocynaceae) (*1–4*).

Synonyms: *Ophioxylon obversum* Miq., *O. sautiferum* Salisb., *O. serpentinum* L., *Rauvolfia obversa* (Miq.) Baill., *R. trifoliata* (Gaertn.) Baill. (*3–5*).

Selected vernacular names: Most commonly called rauwolfia, rauvolfia, sarpagandha, serpentina (*5–8*).

Description: Small, erect, glabrous shrub, 30–60 cm high. Leaves whorled, 7.5–17.5 cm long, lanceolate or oblanceolate, acute or acuminate, tapering gradually into the petiole, thin. Flowers white or pinkish; peduncles 5.0–7.5 cm long; pedicels and calyx red. Calyx lobes 2.5 mm long, lanceolate. Corolla about 1–1.3 cm long; tube slender; inflated slightly above middle; lobes much shorter than tube, obtuse. Drupes about 6 mm (diameter), single or didymous and more or less connate, purplish black when ripe (*1*).

Plant material of interest: root

General appearance: The root occurs as segments 5–15 cm in length and 3–20 mm in diameter, subcylindrical to tapering, tortuous or curved, rarely branched, occasionally bearing twisted rootlets, which are larger, more abundant, and more rigid and woody on the thicker parts of the roots. Externally light brown to grayish yellow to grayish brown, dull, rough, or slightly wrinkled longitudinally, yet smooth to the touch, occasionally showing rootlet scars on the larger pieces, with some exfoliation of the bark in small areas that reveals the paler wood beneath. Bark separates easily from the wood on scraping. Fracture short but irregular, the longer pieces readily breaking with a snap, slightly fibrous marginally. The freshly fractured surfaces show a rather thin layer of grayish yellow bark, and the pale yellowish white wood constitutes about 80% of the radius. The smooth transverse surface of larger pieces shows a finely radiate stele with three or more clearly marked growth rings; a small knob-like protuberance is frequently noticeable in the center. The wood is hard and of relatively low density (*1*).

Organoleptic properties: Root odor is indistinct, earthy, reminiscent of stored white potatoes, and the taste is bitter (*1*).

Microscopic characteristics: A transverse section of the root shows externally 2–8 alternating strata of cork cells, the strata with larger cells alternating with strata made up of markedly smaller cells. Each stratum composed of smaller cells includes 3–5 tangentially arranged cell layers. In the cross-sectional view, the largest cells of the larger cell group measure 40–90 μm radially and up to 75 μm tangentially, while the cells of the smaller group measure 5–20 μm radially and up to 75 μm tangentially. The walls are thin and suberized. The secondary cortex consists of several rows of tangentially elongated to isodiametric parenchyma cells, most densely filled with starch grains; others (short latex cells) occur singly or in short series and contain brown resin masses. The secondary phloem is relatively narrow and is made up of phloem parenchyma (bearing starch grains and less commonly tabular to angular calcium oxalate crystals up to 20 μm in length; also, occasionally, with some brown resin masses in outer cells and phloem rays) interlaid with scattered sieve tissue and traversed by phloem rays 2–4 cells in width. Sclerenchyma cells are absent in root (a distinction from other *Rauvolfia* species). Cambium is indistinct, narrow, dark, and wavering. The secondary xylem represents the large bulk of the root and shows one or more prominent annual rings with a dense core of wood about 500 μm across at the center. The xylem is composed of many wood wedges separated by xylem rays and on closer examination reveals

vessels in interrupted radial rows, much xylem parenchyma, many large-celled xylem rays, few wood fibers, and tracheids, all with lignified walls. The xylem fibers occur in both tangential and radial rows. The xylem rays are 1–12, occasionally up to 16 cells in width (*1*, *3*).

Powdered plant material: Powdered Radix Rauwolfiae is brownish to reddish gray. Numerous starch grains (simple, 2- to 3-compound, occasionally 4-compound) present; simple grains spheroid, ovate, plano- to angular-convex, or irregular; hilum simple, Y-shaped, stellate, or irregularly cleft; unaltered grains 6–34 μm in diameter; altered grains up to about 50 μm; large unaltered grains clearly show polarization cross; calcium oxalate prisms and cluster crystals scattered, about 10–15 μm in size; brown resin masses and yellowish granular secretion masses occur occasionally; isolated cork cells elongated, up to 90 μm in length; phelloderm and phloem parenchyma cells similar in appearance; vessels subcylindrical, up to 360 μm in length and about 20–57 μm in diameter, the vessel end walls oblique to transverse, generally with openings in the end walls, some vessels showing tyloses; tracheids pitted, with moderately thick, tapering, beaded walls, with relatively broad lumina, polygonal in cross section; xylem parenchyma cells with moderately thick walls with simple circular pits, cells polygonal in cross section, bearing much starch, sometimes with brown resin masses; xylem fibers with thick heavily lignified walls showing small transverse and oblique linear pits and pointed simple to bifurcate ends, measuring about 200–750 μm in length. No phloem fibers or sclereids are present in root (colorless non-lignified pericycle or primary phloem fibers, single or in small groups, may be present from rhizome or stem tissues) (*1*).

Geographical distribution: The plant is found growing wild in the sub-Himalayan tracts in India and is also found in Indonesia, Myanmar, and Thailand (*3*). Overcollection of Radix Rauwolfiae in India has significantly diminished supply, and since 1997, there has been an embargo on the export of this drug from India. Reserpine is currently either extracted from the roots of *Rauvolfia vomitoria* of African origin or produced by total synthesis.

General identity tests: Macroscopic and microscopic examinations (*1–3*) and thin-layer chromatographic analysis for the presence of characteristic indole alkaloids (*2*, *3*).

Purity tests

Microbiology: The test for *Salmonella* spp. in Radix Rauwolfiae products should be negative. The maximum acceptable limits of other microorganisms are as follows (*9–11*). For the preparation of decoction: aerobic bacteria, not more than 10^7/g; molds and yeast, not more than 10^4/g; *Escherichia coli,* not more than 10^2/g; other enterobacteria, not more than 10^4/g. Preparations for internal use: aerobic bacteria, not more than 10^5/g; molds and yeast, not more than 10^3/g; *Escherichia coli,* not more than 10^1/g; other enterobacteria, not more than 10^3/g.

Foreign organic matter: Not more than 2.0% of stems and not more than 3.0% of other foreign organic matter (*1*).

Total ash: Not more than 10% (*2*).

Acid-insoluble ash: Not more than 2.0% (*1*, *2*).

Moisture: Not more than 12% (*2*).

Pesticide residues: To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Radix Rauwolfiae is not more than 0.05 mg/kg (*11*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*9*) and guidelines for predicting dietary intake of pesticide residues (*12*).

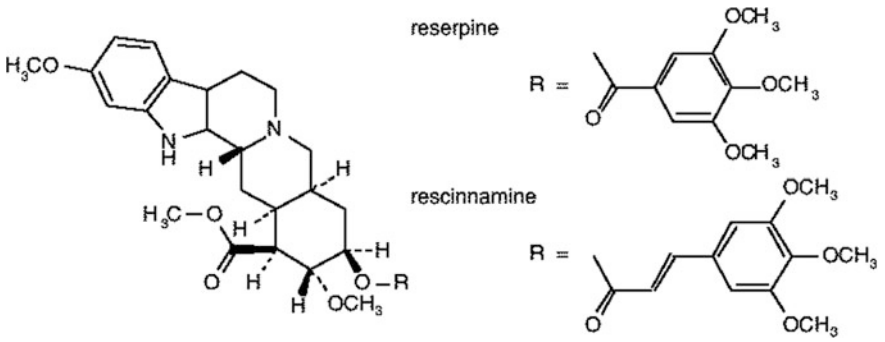
Heavy metals: Recommended lead and cadmium levels are no more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (*9*).

Radioactive residues: For analysis of strontium-90, iodine-131, cesium-134, cesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*9*).

Other purity tests: Chemical, alcohol-soluble extractive, and water-soluble extractive tests to be established in accordance with national requirements.

Chemical assays: Contains not less than 1% total alkaloids (*2*, *3*) and a minimum of 0.1% alkaloids of the reserpine–rescinnamine group (*3*). Thin-layer chromatography to detect the presence of the reserpine–rescinnamine group of alkaloids (*2*, *3*, *13*). Quantitative analysis of total and reserpine–rescinnamine group of alkaloids can be performed by spectrophotometric analysis (*2*, *3*) or by high-performance liquid chromatography (*14*, *15*).

Major chemical constituents: Radix Rauwolfiae contains more than 60 indole alkaloids; the principal hypotensive alkaloids are identified as reserpine and rescinnamine (*1*, *6*).



Dosage forms: Crude drug and powder. Package in well-closed containers and store at 15–25 °C (*9*) in a dry place, secure against insect attack (*1*).

Medicinal uses

Uses supported by clinical data: The principal use today is in the treatment of mild essential hypertension (*16–22*). Treatment is usually administered in combination with a diuretic agent to support the drug's antihypertensive activity and to prevent fluid retention which may develop if Radix Rauwolfiae is given alone (*18*).

Uses described in pharmacopoeias and in traditional systems of medicine: As a tranquilizer for nervous and mental disorders (*4*, *5*).

Uses described in folk medicine, not supported by experimental or clinical data: As a tonic in states of asthenia, a cardiotonic and antipyretic; against snake and insect bites; and for constipation, liver diseases, flatulence, insomnia, and rheumatism (*8*).

Pharmacology

Experimental pharmacology: It is well accepted that the pharmacological effects of Radix Rauwolfiae are due to its alkaloids, especially the reserpine–rescinnamine group. The experimental pharmacology of reserpine and related compounds has been well documented (*5*, *16–18*, *23*). Powdered Radix Rauwolfiae, as well as various forms of extracts (ethanolic, dried), has been reported to lower the blood pressure of experimental animals (dogs or cats) by various routes of administration (*5*).

Clinical pharmacology: Radix Rauwolfiae and its major alkaloids probably lower high blood pressure by depleting tissue stores of catecholamines (epinephrine and norepinephrine) from peripheral sites. By contrast, their sedative and tranquilizing properties are thought to be related to depletion of catecholamines and serotonin (5-hydroxytryptamine) from the brain. Following absorption from the gastrointestinal tract, the active alkaloids concentrate in tissues with high lipid content. They pass the blood–brain barrier and the placenta. Radix Rauwolfiae products are characterized by the slow onset of action and sustained effect. Both the cardiovascular and central nervous system effects may persist following the withdrawal of the drug. The active alkaloids are metabolized in the liver to inactive compounds that are excreted primarily in the urine. Unchanged alkaloids are excreted primarily in the feces (*16*).

Contraindications: Radix Rauwolfiae products are contraindicated in patients who have previously demonstrated hypersensitivity to the plant or its alkaloids. They are also contraindicated in patients with a history of mental depression (especially those with suicidal tendencies) during or shortly after therapy with monoamine oxidase inhibitors; active peptic ulcer, sinus node disorders, ulcerative colitis; epilepsy; or decreased renal function and in patients receiving electroconvulsive therapy (*16*, *18*).

Warnings: Radix Rauwolfiae products may cause mental depression (*24*). Recognition of depression may be difficult because this condition may often be disguised by somatic complaints (masked depression). The products should be discontinued at first signs of depression such as despondency, early morning insomnia, loss of appetite, impotence, or self-deprecation. Drug-induced depression may persist for several months after drug withdrawal and may be severe enough to result in suicide. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. The use of Radix Rauwolfiae products may impair alertness and make it inadvisable to drive or operate heavy machinery (*16*, *18*).

Precautions

General: Because Radix Rauwolfiae preparations increase gastrointestinal motility and secretion, they should be used cautiously in persons with a history of peptic ulcer, ulcerative colitis, or gallstones where biliary colic may be precipitated. Persons on high doses should be observed carefully at regular intervals to detect possible reactivation of peptic ulcer (*16*).

Caution should be exercised when treating hypertensive patients with renal insufficiency since they adjust poorly to lowered blood pressure levels (*16*).

Drug interactions: When administered concurrently, the following drugs may interact with or potentiate Radix Rauwolfiae and its alkaloids (*16*, *18*): alcohol or other central nervous system depressants, other antihypertensives or diuretics, digitalis glycosides or quinidine, levodopa, levomepromazine, monoamine oxidase inhibitors, sympathomimetics (direct-acting), and tricyclic antidepressants. Concomitant use of Radix Rauwolfiae products and anesthetics may provoke a fall in blood pressure (*4*, *17*, *25*) and add to the β-adrenoceptor blocking activity of propranolol (*25*).

Drug and laboratory test interactions: Chronic administration of Radix Rauwolfiae preparations may increase serum prolactin levels and decrease excretion of urinary catecholamines and vanilmandelic acid. Therefore, any diagnostic tests performed for these determinations should be interpreted with caution (*16*). Radix Rauwolfiae preparations slightly decrease absorbance readings obtained on urinary steroid colorimetric determinations (e.g., modified Glenn–Nelson technique or Holtorff-Koch modification of Zimmermann reaction), and thus, false low results may be reported (*16*). Preoperative withdrawal of Radix Rauwolfiae products does not necessarily ensure circulatory stability during the procedure, and the anesthetist must be informed of the patient's drug history (*4*, *17*, *25*). Caution is indicated in elderly patients and also in those suffering from coronary and cerebral arteriosclerosis. Administration of products including Radix Rauwolfiae preparations at doses that might precipitate a sharp decrease in blood pressure should be avoided (*17*).

Carcinogenesis, **mutagenesis, impairment of fertility**: Animal carcinogenicity studies using reserpine at doses 50 times as high as the average human dose have been conducted with rats and mice. Carcinogenic effects associated with the administration of reserpine include an increased incidence of adrenal medullary pheochromocytomas in male rats, unidentified carcinomas of the seminal vesicles in male mice, and mammary cancer in female mice; carcinogenic effects were not seen in female rats (*14*, *23*, *26*). Bacteriological studies to determine mutagenicity using reserpine showed negative results (*16*). The extent of risk to humans is uncertain (*16*, *26–28*).

Pregnancy: teratogenic effects: Reserpine, the major active alkaloid in Radix Rauwolfiae, administered parenterally has been shown to be teratogenic in rats at doses up to 2 mg/kg and to have an embryocidal effect in guinea-pigs at 0.5 mg daily (*27*). There are no adequate and well-controlled studies in pregnant women.

Pregnancy: non-teratogenic effects: Increased respiratory secretions, nasal congestion, cyanosis, hypothermia, and anorexia have occurred in neonates of mothers treated with Radix Rauwolfiae (*16*, *28*, *29*). Therefore, the use of Radix Rauwolfiae is not recommended during pregnancy.

Nursing mothers: Rauwolfia alkaloids are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, use of Radix Rauwolfiae during lactation is not recommended.

Pediatric use: Safety and effectiveness in children have not been established (*16*).

Adverse reactions: The following adverse reactions have been observed, but there are insufficient data to support an estimate of their frequency. The reactions are usually reversible and disappear when the Radix Rauwolfiae preparations are discontinued (*16*, *18*). Cardiovascular system: bradycardia, arrhythmias, particularly when used concurrently with digitalis or quinidine, angina-like symptoms. Water retention with edema in persons with hypertensive vascular disease may occur rarely, but the condition generally clears with cessation of therapy or the administration of a diuretic agent. Vasodilation produced by rauwolfia alkaloids may result in nasal congestion, flushing, a feeling of warmth, and conjunctival congestion. Central nervous system: sensitization of the central nervous system manifested by optic atrophy, glaucoma, uveitis, deafness, and dull sensorium. Other reactions include depression, paradoxical anxiety, nightmares, nervousness, headache, dizziness, drowsiness. Large doses have produced parkinsonian syndrome, other extrapyramidal reactions, and convulsions. Gastrointestinal system: hypersecretion and increased intestinal motility, diarrhea, vomiting, nausea, anorexia, and dryness of mouth. Gastrointestinal bleeding has occurred in isolated cases. Respiratory system: dyspnea, epistaxis, nasal congestion. Hypersensitivity: purpura, pruritus, rash. Other: dysuria, muscular aches, weight gain, breast engorgement, pseudolactation, impotence or decreased libido, gynecomastia.

Posology: Powder, 200 mg daily in divided doses for 1–3 weeks; maintenance 50–300 mg daily (*1*). Doses of other preparations should be calculated accordingly. Doses of Radix Rauwolfiae should be based on the recommended dosage of rauwolfia alkaloids, which must be adjusted according to the patient's requirements and tolerance in small increments at intervals of at least 10 days. Debilitated and geriatric patients may require lower dosages of rauwolfia alkaloids than do other adults (*18*). Rauwolfia alkaloids may be administered orally in a single daily dose or divided into two daily doses (*18*).

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7.6.4 Rhizoma Zingiberis

Definition: Rhizoma Zingiberis is the dried rhizome of *Zingiber officinale* Roscoe (*Zingiberaceae*) (*1–5*)

Synonyms: *Amomum zingiber* L. (*1*, *6*), *Zingiber blancoi* Massk. (*6*).

Selected vernacular names: Ada, adrak, African ginger, common ginger (*1*, *4*, *6–13*).

Description: A perennial herb with a subterranean, digitately branched rhizome producing stems up to 1.50 m in height with linear lanceolate sheathing leaves (5–30 cm long and 8–20 mm wide) that are alternate, smooth, and pale green. Flower stems shorter than leaf stems and bearing a few flowers, each surrounded by a thin bract and situated in axils of large, greenish yellow obtuse bracts, which are closely arranged at end of flower stem forming collectively an ovate-oblong spike. Each flower shows a superior tubular calyx, split part way down one side; an orange yellow corolla composed of a tube divided above into three linearoblong, blunt lobes; six staminodes in two rows, the outer row of three inserted at mouth of corolla; the posterior two, small, horn-like; the anterior petaloid, purple and spotted and divided into three rounded lobes; an inferior, 3-celled ovary with tufted stigma. Fruit a capsule with small arillate seeds (*1*, *7*, *8*).

Plant material of interest: dried rhizome

General appearance: Ginger occurs in horizontal, laterally flattened, irregularly branching pieces; 3–16 cm long, 3–4 cm wide, up to 2 cm thick; sometimes split longitudinally; pale yellowish buff or light brown externally, longitudinally striated, somewhat fibrous; branches known as 'fingers' arise obliquely from the rhizomes, are flattish, obovate, short, about 1–3 cm long; fracture, short, and starchy with projecting fibers. Internally, yellowish brown, showing a yellow endodermis separating the narrow cortex from the wide stele, and numerous scattered fibrovascular bundles, abundant scattered oleoresin cells with yellow contents and numerous larger grayish points, vascular bundles, scattered on the whole surface (*1–5*).

Organoleptic properties: Odor, characteristic aromatic; taste, pungent, and aromatic (*1–5*); color, internally pale yellow to brown (*1*, *4*).

Microscopic characteristics: Cortex of isodiametric, thin-walled parenchyma cells contains abundant starch granules, each with a pointed hilum up to 50 μm long and 25 μm wide and 7 μm thick, and showing scattered secretion cells with suberized walls and yellowish brown oleoresinous content, and scattered bundles of the leaf-traces accompanied by fibers; endodermis, of pale brown, thin-walled cells with suberized radial walls; stele, with parenchymatous ground tissue, numerous yellow oleoresin secretion cells and numerous scattered, closed collateral vascular bundles with non-lignified, reticulate, scalariform, and spiral vessels, often accompanied by narrow cells; containing a dark brown pigment, and supported by thin-walled fibers with wide lumen, small oblique slit-like pits, and lignified middle lamella; some of the fibers are septate (*1*, *3*, *4*).

Powdered plant material: Powdered ginger is yellowish white to yellowish brown; characterized by numerous fragments of thin-walled parenchyma cells containing starch granules; fragments of thin-walled septate fibers with oblique slit-like pits; fragments of non-lignified scalariform, reticulate, and spiral vessels, often accompanied by dark pigment cells; oleoresin in fragments or droplets with oil cells and resin cells scattered in parenchyma; numerous starch granules, simple, flat, oval, oblong with terminal protuberance, in which the hilum is pointed, 5–60 μm usually 15–30 μm long, 5–40 μm (usually 18–25 μm) wide, 6–12 μm (usually 8–10 μm) thick with somewhat marked fine transverse striations (*1–4*).

Geographical distribution: The plant is probably native to Southeast Asia and is cultivated in the tropical regions in both the eastern and western hemispheres. It is commercially grown in Africa, China, India, and Jamaica; India is the world's largest producer (*1*, *4*, *6*, *7*, *10*, *14*).

General identity tests: Rhizoma Zingiberis is identified by its macroscopic and organoleptic characteristics, including its characteristic form, color, pungent taste, and volatile oil content and by microchemical tests (*1–5*).

Purity tests

Microbiology: The test for *Salmonella* spp. in Rhizoma Zingiberis products should be negative. The maximum acceptable limits of other microorganisms are as follows (*15–17*). For the preparation of decoction: aerobic bacteria, not more than 10^7/g; fungi, not more than 10^5/g; *Escherichia coli,* not more than 10^2/g. Preparations for internal use: aerobic bacteria, not more than 10^5/g or ml; fungi, not more than 10^4/g or ml; enterobacteria and certain Gram-negative bacteria, not more than 10^3/g or ml; *Escherichia coli,* 0/g or ml.

Foreign organic matter: Not more than 2.0% (*1*). Powdered ginger is frequently adulterated with exhausted ginger (*8*).

Total ash: Not more than 6.0% (*2*, *3*).

Acid-insoluble ash: Not more than 2.0% (*5*).

Water-soluble extractive: Not less than 10% (*3*, *4*).

Alcohol-soluble extractive: Not less than 4.5% (3).

Pesticide residues: To be established in accordance with national requirements. Normally, the maximum residue limit of aldrin and dieldrin in Rhizoma Zingiberis is not more than 0.05 mg/kg (*17*). For other pesticides, see WHO guidelines on quality control methods for medicinal plants (*15*) and guidelines for predicting dietary intake of pesticide residue (*18*).

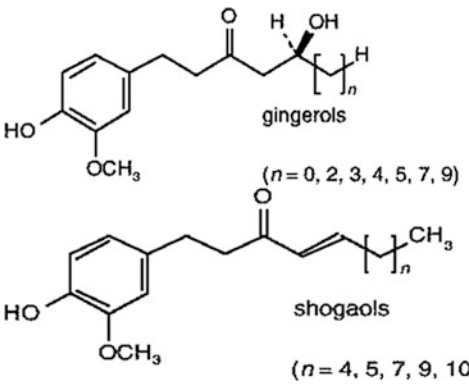
Heavy metals: Recommended lead and cadmium levels are not more than 10 and 0.3 mg/kg, respectively, in the final dosage form of the plant material (15).

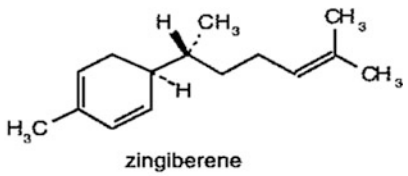
Radioactive residues: For analysis of strontium-90, iodine-131, cesium-134, cesium-137, and plutonium-239, see WHO guidelines on quality control methods for medicinal plants (*15*).

Other purity tests: Chemical and moisture tests to be established in accordance with national requirements.

Chemical assays: Contains not less than 2% v/w of volatile oil (*1*), as determined by the method described in WHO guidelines (*15*). Qualitative analysis by thin-layer chromatography (*1*); qualitative and quantitative gas chromatography and high-performance liquid chromatography analyses of ginger oils for gingerols, shogaols, α-zingiberene, β-bisabolene, β-sesquiphellandrene, and *ar*-curcumene (*19*).

Major chemical constituents: The rhizome contains 1–4% essential oil and an oleoresin. The composition of the essential oil varies as a function of geographical origin, but the chief constituent sesquiterpene hydrocarbons (responsible for the aroma) seem to remain constant. These compounds include (−)-zingiberene, (+)-*ar*-curcumene, (−)-β-sesquiphellandrene, and β-bisabolene. Monoterpene aldehydes and alcohols are also present. The constituents responsible for the pungent taste of the drug and possibly part of its antiemetic properties have been identified as 1-(3′-methoxy-4′-hydroxyphenyl)-5-hydroxyalkan-3-ones, known as [3–6]-, [8]-, [10]-, and [12]-gingerols (having a side chain with 7–10, 12, 14, or 16 carbon atoms, respectively) and their corresponding dehydration products, which are known as shogaols (*1*, *4*, *6*, *14*, *19*). Representative structures of zingiberene, gingerols, and shogaols are presented below.





Dosage forms: Dried root powder, extract, tablets, and tincture (*2*, *14*). Powdered ginger should be stored in well-closed containers (not plastic) which prevent access of moisture. Store protected from light in a cool, dry place (*4*, *5*).

Medicinal uses

Uses supported by clinical data: The prophylaxis of nausea and vomiting associated with motion sickness (20–23), postoperative nausea (24), pernicious vomiting in pregnancy (25), and seasickness (26, 27).

Uses described in pharmacopoeias and in traditional systems of medicine: The treatment of dyspepsia, flatulence, colic, vomiting, diarrhea, spasms, and other stomach complaints (*1*, *2*, *4*, *9*, *21*). Powdered ginger is further employed in the treatment of colds and flu, to stimulate the appetite, as a narcotic antagonist (*1*, *2*, *4*, *6*, *11*, *12*, *21*) and as an anti-inflammatory agent in the treatment of migraine headache and rheumatic and muscular disorders (*9*, *11*, *12*, *28*).

Uses described in folk medicine, not supported by experimental or clinical data: To treat cataracts, toothache, insomnia, baldness, and hemorrhoids and to increase longevity (9, 10, 12).

Pharmacology
Experimental pharmacology

Cholagogic activity: Intraduodenal administration of an acetone extract (mainly essential oils) of ginger root to rats increased bile secretion for 3 h after dosing, while the aqueous extract was not active (*29*). The active constituents of the essential oil were identified as [6]- and [10]-gingerol (*29*). Oral administration of an acetone extract of ginger (75 mg/kg), [6]-shogaol (2.5 mg/kg), or [6]-, [8]-, or [10]-gingerol enhanced gastrointestinal motility in mice (*30*), and the activity was comparable to or slightly weaker than that of metoclopramide (10 mg/kg) and domperidone (*30*). The [6]-, [8]-, or [10]-gingerols are reported to have antiserotoninergic activity, and it has been suggested that the effects of ginger on gastrointestinal motility may be due to this activity (*30*, *31*). The mode of administration appears to play a critical role in studies on gastrointestinal motility. For example, both [6]-gingerol and [6]-shogaol inhibited intestinal motility when administered intravenously but accentuated gastrointestinal motility after oral administration (*6*, *12*, *32*).

Antiemetic activity: The emetic action of the peripherally acting agent copper sulfate was inhibited in dogs given an intragastric dose of ginger extract (*33*), but emesis in pigeons treated with centrally acting emetics such as apomorphine and digitalis could not be inhibited by a ginger extract (*34*). These results suggest that ginger's antiemetic activity is peripheral and does not involve the central nervous system (*11*). The antiemetic action of ginger has been attributed to the combined action of zingerones and shogaols (*11*).

Anti-inflammatory activity: One of the mechanisms of inflammation is increased oxygenation of arachidonic acid, which is metabolized by cyclooxygenase and 5-lipoxygenase, leading to prostaglandin E_2 and leukotriene B_4, two

potent mediators of inflammation (*28*). In vitro studies have demonstrated that a hot-water extract of ginger inhibited the activities of cyclooxygenase and lipoxygenase in the arachidonic acid cascade; thus, its anti-inflammatory effects may be due to a decrease in the formation of prostaglandins and leukotrienes (*35*). The drug was also a potent inhibitor of thromboxane synthase and raised prostacyclin levels without a concomitant rise in prostaglandins E_2 or $F_{2\alpha}$ (*36*). In vivo studies have shown that oral administration of ginger extracts decreased rat paw edema (*37*, *38*). The potency of the extracts was comparable to that of acetylsalicylic acid. [6]-Shogaol inhibited carrageenan-induced paw edema in rats by inhibiting cyclooxygenase activity (*39*). Recently, two labdane-type diterpene dialdehydes isolated from ginger extracts have been shown to be inhibitors of human 5-lipoxygenase in vitro (*40*).

Clinical pharmacology

Antinausea and antiemetic activities: Clinical studies have demonstrated that oral administration of powdered ginger root (940 mg) was more effective than dimenhydrinate (100 mg) in preventing the gastrointestinal symptoms of kinetosis (motion sickness) (*22*). The results of this study further suggested that ginger did not act centrally on the vomiting center, but had a direct effect on the gastrointestinal tract through its aromatic, carminative, and absorbent properties, by increasing gastric motility and adsorption of toxins and acids (*22*).

In clinical double-blind randomized studies, the effect of powdered ginger root was tested as a prophylactic treatment for seasickness (*26*, *27*). The results of one study demonstrated that orally administered ginger was statistically better than a placebo in decreasing the incidence of vomiting and cold sweating 4 h after ingestion (*27*). The other investigation compared the effects of seven over-the-counter and prescription antiemetic drugs on prevention of seasickness in 1489 subjects. This study concluded that ginger was as effective as the other antiemetic drugs tested (*26*).

At least eight clinical studies have assessed the effects of ginger root on the symptoms of motion sickness. Four of these investigations showed that orally administered ginger root was effective for prophylactic therapy of nausea and vomiting. The other three studies showed that ginger was no more effective than a placebo in treating motion sickness (*23*, *41*, *42*). The conflicting results appear to be a function of the focus of these studies. Clinical studies that focused on the gastrointestinal reactions involved in motion sickness recorded better responses than those studies that concentrated primarily on responses involving the central nervous system.

The hypothesis that an increase in gastric emptying may be involved in the antiemetic effects of ginger has recently come under scrutiny. Two clinical studies demonstrated that oral doses of ginger did not affect the gastric emptying rate, as measured by sequential gastric scintigraphy (*43*) or the paracetamol absorption technique (*44*).

In a double-blind, randomized, cross-over trial, oral administration of powdered ginger (250 mg, 4 times daily) effectively treated pernicious vomiting in pregnancy

(*25*). Both the degree of nausea and the number of vomiting attacks were significantly reduced (*25*). Furthermore, in a prospective, randomized, double-blind study, there were statistically significantly fewer cases of postoperative nausea and vomiting in 60 patients receiving ginger compared to a placebo (*24*). The effect of ginger on postoperative nausea and vomiting was reported to be as good as or better than that of metoclopramide (*24*, *45*). In contrast, another double-blind randomized study concluded that orally administered ginger BP (prepared according to the British pharmacopoeia) was ineffective in reducing the incidence of postoperative nausea and vomiting (*46*).

Anti-inflammatory activity: One study in China reported that 113 patients with rheumatic pain and chronic lower back pain, injected with a 5–10% ginger extract into the painful points or reaction nodules, experienced full or partial relief of pain, decrease in joint swelling, and improvement or recovery in joint function (*11*). Oral administration of powdered ginger to patients with rheumatism and musculoskeletal disorders has been reported to provide varying degrees of relief from pain and swelling (*28*).

Contraindications: No information available.

Warnings: No information available.

Precautions

General: Patients taking anticoagulant drugs or those with blood coagulation disorders should consult their physician prior to self-medication with ginger. Patients with gallstones should consult their physician before using ginger preparations (*21*).

Drug interactions: Ginger may affect bleeding times and immunological parameters owing to its ability to inhibit thromboxane synthase and to act as a prostacyclin agonist (*47*, *48*). However, a randomized, double-blind study of the effects of dried ginger (2 g daily, orally for 14 days) on platelet function showed no differences in bleeding times in patients receiving ginger or a placebo (*49*, *50*). Large doses (12–14 g) of ginger may enhance the hypothrombinemic effects of anticoagulant therapy, but the clinical significance has yet to be evaluated.

Carcinogenesis, mutagenesis, impairment of fertility: The mutagenicity of ginger extracts is a controversial subject. A hot-water extract of ginger was reported to be mutagenic in B291I cells and *Salmonella typhimurium* strain TA 100, but not in strain TA 98 (*51*). A number of constituents of fresh ginger have been identified as mutagens. Both [6]-gingerol and shogaols have been determined to be mutagenic in a *Salmonella*/microsome assay (*52*), and increased mutagenesis was observed in an Hs30 strain of *Escherichia coli* treated with [6]-gingerol (*53*). However, the mutagenicity of [6]-gingerol and shogaols was suppressed in the presence of various concentrations of zingerone, an antimutagenic constituent of ginger (*52*). Furthermore, ginger juice was reported to be antimutagenic and suppressed the spontaneous mutations induced by [6]-gingerol, except in cases where the mutagenic chemicals 2-(2-furyl)-3-(5-nitro-2-furyl)acryl amide and *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine were added to [6]-gingerol (*54*). Other investigators have also reported that ginger juice is antimutagenic (*54, 55*).

Pregnancy: teratogenic effects: In a double-blind randomized cross-over clinical trial, ginger (250 mg by mouth, 4 times daily) effectively treated pernicious vomiting in pregnancy (*25*). No teratogenic aberrations were observed in infants born during this study, and all newborn babies had Apgar scores of 9 or 10 after 5 min (*25*).

Pediatric use: Not recommended for children less than 6 years of age.

Other precautions: No information available concerning drug and laboratory test interactions, or non-teratogenic effects on pregnancy or nursing mothers.

Adverse reactions: Contact dermatitis of the finger tips has been reported in sensitive patients (*56*).

Posology: For motion sickness in adults and children more than 6 years: 0.5 g, 2–4 times daily. Dyspepsia, 2–4 g daily, as powdered plant material or extracts (*21*).

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7.7 Monographs of Unorganized Drugs

The unorganized drugs consist of some natural substances, which are derived from plants and animals by a number of extraction processes like incision, decoction, expression, distillation, and percolation or as natural secretions. Thus, these drugs are devoid of definite histological or cellular structures, i.e., they are not built up into any definite plant or animal organs. They represent both physiological and pathological products of plants and animals, and occur as solids, semi-solids, and liquids depending on the type of the products constituting the drug.

The unorganized drugs may be classified into the following groups on the basis of their origin and nature such as latices (opium, papain), juices (aloe, kino), extracts (agar, catechu, curare), gums (acacia, tragacanth, sterculia), resins (colophony, guaiacum, benzoins, gamboge, myrrh, asafetida, copaiba), balsams (Canada balsam, tolu balsam, Peru balsam, storax), fixed oils and fats (olive oil, castor oil), and volatile oils (clove oil, cinnamon oil, lemon oil). Some of these unorganized drugs of these groups are described below in the form of monographs as per WHO guidelines.

Oleum Azadirachti

Definition: Oleum Azadirachti consists of the fixed oil obtained from dried seeds of *Azadirachta indica* A. Juss. (Meliaceae).

Synonyms: *Melia azadirachta* L., *M. indica* (A. Juss.) Brand., *M. indica* Brand. (*1–3*).

Selected vernacular names: Indian lilac, Indian lilac tree, Indian neem tree, (*1–9*).

Geographical distribution: Indigenous to India and widely distributed in South and Southeast Asia. Cultivated in Africa, the South Pacific Islands, South and Central America and Australia, and in southern Florida and California, USA (*1–3, 7, 10, 11*).

Description: A straight-boled deciduous tree 6–25 m high. Bark dark brown, externally fissured, with a buff inner surface, fibrous fracture. Leaves alternately arranged, pinnately compound, up to 40 cm long, composed of 8–18 short-petiolate narrow-ovate, pointed, curved toothed leaflets, 3–10 cm long and 1–4 cm wide arranged in alternate pairs. Inflorescences axillary panicles; flowers numerous, white, pedicellate, about 1.0 cm wide. Fruits yellowish drupes, oblong, about 1.5 cm long, containing thin pulp surrounding a single seed. When bruised, leaves and twigs emit an onion-like odor (*1–3, 7, 11*).

Plant material of interest: fixed oil

General appearance: No information available.

Organoleptic properties: Odor: characteristic alliaceous (*10*); taste: no information available.

General identity tests: Macroscopic examination and thin-layer chromatography (*2*).

Purity tests

Microbiological: Tests for specific microorganisms and microbial contamination limits are as described in the WHO guidelines on quality control methods for medicinal plants (12).

Chemical: Relative density 0.913–0.919 (13); refractive index 1.462–1.466 (13); saponification value 196.0 (13).

Pesticide residues: The recommended maximum limit of aldrin and dieldrin is not more than 0.05 mg/kg (*14*). For other pesticides, see the *European pharmacopoeia* (*14*) and the WHO guidelines on quality control methods for medicinal plants (*12*) and pesticide residues (*15*).

Heavy metals: For maximum limits and analysis of heavy metals, consult the WHO guidelines on quality control methods for medicinal plants (12).

Radioactive residues: Where applicable, consult the WHO guidelines on quality control methods for medicinal plants (*12*) for the analysis of radioactive isotopes.

Chemical assays: A high-performance liquid chromatography procedure is available for the quantitative determination of oxidized tetranortriterpenes (*16*).

Major chemical constituents: The major constituents are oxidized tetranortriterpenes including azadirachtin (azadirachtin A), azadiradione, epoxyazadiradione, azadirone, nimbidin, nimbin, deacetylnimbin, salannin, gedunin, mahmoodin, 17-hydroxydiradione, and related derivatives (*9, 11, 17–19*). The structures of azadirachtin, nimbin, and deacetylnimbin are presented below:

Medicinal uses

Uses supported by clinical data: As a contraceptive for intravaginal use (20), as a mosquito repellent (21), and for the treatment of vaginal infections (22). However, further controlled clinical trials are needed before the oil can be recommended for general use.

Uses described in pharmacopoeias and well-established documents: Treatment of gastric ulcers, cardiovascular disease, malaria, rheumatism, and skin disorders. External applications for treatment of septic wounds, ulcers, and boils (7).

Uses described in traditional medicine: Treatment of allergic skin reactions, asthma, bruises, colic, conjunctivitis, dysmenorrhea, fever, gout, headache, itching due to varicella, kidney stones, leukorrhea, psoriasis, scabies, sprains and muscular pain, and wounds (10, 11). As an emmenagogue, tonic, stomatic, and vermicide (9).

Pharmacology

Experimental pharmacology

Antifertility activity: Oleum Azadirachti, 0.6 ml, was given to female rats by intragastric administration on days 8–10 of pregnancy, after confirming the presence and number of embryo implants surgically on day 7. The animals were examined again under anesthesia on day 15 of pregnancy to check the number of developing embryos. Controls received an equivalent regime of peanut oil. Complete resorption of embryos was observed on day 15 of pregnancy in every animal treated with Oleum Azadirachti, while embryos were developing normally in controls (*23*). Intragastric administration of 6.0 ml of the oil per day for 60 days to female baboons induced abortion in pregnant animals (*24*). A single intrauterine application of 100.0 μl of the oil produced a reversible block in fertility lasting for 107–180 days in female rats (*25*) and 7–11 months in monkeys (*26*). In an attempt to find an alternative to vasectomy for long-term male contraception, the effect of a single intra-vas application of the oil was assessed in male rats. Animals with proven fertility were given a single dose of 50.0 μl of the oil in the lumen of the vas deferens on each side. Control animals received the same volume of peanut oil. Animals were allowed free access to mating for 4 weeks after the treatment, with females of proven fertility. While the control animals impregnated their female partners, all males treated with Oleum Azadirachti remained infertile throughout the eight-month observation period. Epididymal and vas histologies were normal, with no inflammatory changes or obstruction. Intra-vas administration of the oil resulted in a block of spermatogenesis without affecting testosterone production. The seminiferous tubules, although reduced in diameter, appeared normal and contained mostly early spermatogenic cells. No anti-sperm antibodies were detected in the serum (27). Subcutaneous administration of up to 0.3 ml of the oil to rats had no estrogenic, anti-estrogenic, or progestational activity and appeared not to interfere with the action of progesterone (28). Intravaginal application of 2.50 μl–0.25 ml of the oil to pregnant rats induced abortion (29). The oil, 10–25%, inhibited fertilization in isolated mouse ova as assessed by sperm–egg interaction, and impaired the development of fertilized ova in vitro (30). In other investigations, the active constituents of the oil were identified to be a mixture of six compounds comprising saturated, mono-, and di-unsaturated free fatty acids and their methyl esters (31). The oil, 0.25–25.00 mg/ml, had spermicidal effects on human and rat sperm in vitro (32, 33).

Antihyperglycemic activity: Intragastric administration of 21.0 mg/kg body weight (bw) of the oil reduced blood glucose levels in rats (*34*). A significant ($P < 0.01$) reduction in blood glucose levels was observed in normal and alloxan-induced diabetic rabbits after administration of 200.0 mg of the oil; the effect was more pronounced in diabetic animals (*35*).

Anti-inflammatory activity: The anti-inflammatory effects of nimbidin were assessed and compared with phenylbutazone. Intramuscular administration of 40.0 mg/kg bw of nimbidin reduced acute paw edema in rats induced by carrageenan and kaolin. Formalin-induced arthritis in ankle joints and fluid exudation due to granuloma induced by croton oil in rats were also suppressed by similar treatment with the compound. In the acute phase of inflammation, nimbidin at 40.0 mg/kg bw was more active than phenylbutazone at 100.0 mg/kg bw (*36*). Intramuscular administration of 50.0 mg/kg bw of the oil reduced granuloma induced by cotton pellet in rats (37).

Antimicrobial and antiviral activity: The efficacy of a petroleum ether extract of the oil was investigated for its antimicrobial activity against certain bacteria and fungi and poliovirus, as compared with the oil. The extract had stronger antimicrobial activity than the oil and, in vitro at 2.0 mg/ml, inhibited the growth of *Escherichia coli* and *Klebsiella pneumoniae*, which were not inhibited by the oil. The extract was active against *Candida albicans* (minimum inhibitory concentration 0.25 mg/ml) and had antiviral activity against poliovirus replication in Vero African green monkey kidney cell lines at 50.0 μg/ml (*38*). Intravenous administration of 60.0 mg/kg bw of the oil twice per day for 7 days protected mice from systemic candidiasis, as shown by enhanced survival and a reduction in colony-forming units of *C. albicans* in various tissues (*38*). The oil inhibited the growth of *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus,* and *S. pyogenes* in vitro at a concentration of 1.5–6.0% (39). A petroleum ether extract of the oil inhibited the growth of *Epidermophyton fl occosum, Microsporum canis, M. gypseum, Trichophyton concentricum, T. rubrum,* and *T. violaceum* (40).

Antiulcer activity: Intragastric administration of 40.0 mg/kg bw of nimbidin showed antiulcer activity in various experimental models (gastric lesions induced by acetylsalicylate, stress, serotonin, and indomethacin) in rats. The compound also protected against cysteamine- and histamine-induced duodenal lesions in rodents (41).

Estrogenic activity: Subcutaneous administration of 0.2–6.0 ml/kg bw of the oil to normal or ovariectomized rats had no estrogenic effects: There was no increase in uterine wet weight or disruption of the estrous cycle (*28, 29*).

Immune effects: Mice received Oleum Azadirachti, 150.0 μl/animal, or an emulsifying agent, with or without peanut oil, by intraperitoneal injection. Peritoneal lavage on subsequent days showed an increase in the number of leukocytic cells on day 3 following treatment with Oleum Azadirachti, and peritoneal macrophages exhibited enhanced phagocytic activity and expression of major histocompatibility complex class II antigens. Treatment also induced the production of γ-interferon. The spleen cells of oil-treated animals showed a

significantly higher lymphocyte proliferative response to in vitro challenge with concanavalin A or tetanus toxin than those of controls. Pretreatment with the oil did not augment the anti-tetanus-toxin antibody response. The results of this study indicate that the oil acts as a nonspecific immunostimulant and that it selectively activates cell-mediated immune mechanisms to elicit an enhanced response to subsequent mitogenic or antigenic challenge (*42*). Intraperitoneal administration of the oil to mice (150.0 μl/animal) and rats (120.0 μl/animal) enhanced phagocytosis of macrophages (42, 43).

Toxicology: Studies of the oral acute toxicity of the oil in rats and rabbits showed dose-related pharmacotoxic symptoms along with a number of biochemical and histopathological indices of toxicity. The 24-h oral median lethal dose was 14.0 ml/kg bw in rats and 24.0 ml/kg bw in rabbits. Prior to death, all animals exhibited pharmacotoxic symptoms of a similar type and severity; the lungs and central nervous system were the target organs (*44*). Intragastric administration of the oil to mice was not toxic at a dose of 2.0 ml. The oil (dose not specified) was nonirritant when applied to the skin of rabbits in a primary dermal irritation test. In a subacute dermal toxicity study, rabbits exposed to the oil (dose not specified) daily for 21 days showed no significant changes in body weight or organ: body weight ratio, serum oxaloacetic transaminase and pyruvic transaminase levels, and blood glucose and urea nitrogen values. No treatment-related histopathological changes were observed (*45*). In a three-generation study carried out according to a World Health Organization/US Food and Drug Administration protocol, groups of 15 male and 15 female rats were fed a diet containing 10% Oleum Azadirachti or peanut oil. Reproductive toxicology was monitored for three generations. There were no adverse effects on the reproductive parameters in either group (*46*). A group of 10 pregnant rats received 2.0 ml/kg bw of the oil by gastric administration daily, and the animals were allowed to deliver at term. Six of the treated animals died between days 6 and 13 of pregnancy. Among the four remaining animals that delivered, one delivered a seemingly normal pup on day 27, but the pup died after 4 days. Autopsy performed on day 16 of pregnancy suggested that fetal resorption had occurred; however, no indication was given as to whether fetuses were normal (*47*).

Clinical pharmacology

Contraceptive activity: In an uncontrolled clinical trial involving 225 healthy fertile women aged 18–35 years performed to assess the efficacy of the oil as an antifertility agent, subjects were instructed to insert 1 ml of the oil into the vagina with a plastic applicator 5 min prior to coitus. No other contraception was used. After 16 months of use, only three pregnancies due to drug failure were reported; there were 30 pregnancies due to noncompliance (i.e., in women who did not use the oil as instructed) (*20*).

Antibacterial activity: In a two-week double-blind, placebo-controlled clinical trial involving 55 women with abnormal vaginal discharge due to bacterial vaginosis, subjects were instructed to insert 5.0 ml of the oil or placebo oil into the

vagina daily. Treatment with the test oil was reported to cure the symptoms of the infection (*22*).

Insect repellent activity: In a field study carried out to evaluate the mosquito repellent action of the oil in villages in a forested area in Mandla District, Madhya Pradesh, India, various concentrations of the oil were mixed with coconut oil (1–4%) and applied to the exposed body parts of human volunteers. The mixture provided 81–91% protection from the bites of anopheline mosquitoes during a 12-h period of observation (*21*).

Treatment of skin disorders: In one case report, administration of 100.0 mg of oil twice daily for 34 days completely healed chronic skin ulcers up to 1 cm deep (*48*).

Adverse reactions: A 60-year-old male was admitted to hospital with neurological and psychotic symptoms following ingestion of 60.0 ml of Oleum Azadirachti. However, correlation of the adverse effects with ingestion of the oil was not definitely proven (*49*).

Contraindications: Oral administration of Oleum Azadirachti is contraindicated during pregnancy, nursing, and in children under the age of 12 years.

Warnings: A number of cases of toxicity, including toxic encephalopathy, poisoning, and Reye-like syndrome, following ingestion of excessive doses of Oleum Azadirachti have been reported (*50–52*).

Precautions

Drug interactions: Administration of the oil may reduce blood glucose levels. It should therefore be used with caution in insulin-dependent diabetic patients or patients taking oral antihyperglycemic drugs.

Carcinogenesis, mutagenesis, impairment of fertility: An acetone extract of the oil was inactive at concentrations of up to 200.0 mg/plate in the *Salmonella*/microsome assay using *Salmonellatyphimurium* strains TA98 and TA100 (*53*). In the same test, the oil (concentration not specified) was not mutagenic using *Salmonella typhimurium* strains TA98 and TA100, with or without metabolic activation (*54*). The oil has demonstrated antifertility effects in numerous animal and human studies (see Pharmacology).

Pregnancy: teratogenic effects: The oil had embryotoxic effects after vaginal administration to pregnant rats at a dose of 0.25 ml/animal (*32, 33*). Embryotoxic effects were also reported following intragastric administration of 4.0 ml/kg bw of the oil to pregnant rats on days 6–8 of pregnancy (*47*).

Pregnancy: non-teratogenic effects: See Contraindications.

Nursing mothers: See Contraindications.

Pediatric use: See Contraindications. Oleum Azadirachti.

Other precautions: No information available on general precautions or on precautions concerning drug and laboratory test interactions.

Dosage forms: Oil. Store in a tightly sealed container away from heat and light.

Posology (Unless otherwise indicated): Dose: 1.0–5.0 ml of oil for intravaginal applications (*20, 22*).

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7.8 Monographs of Some Drugs from Animal Sources

A large number of natural products of pharmaceutical and medicinal importance are obtained from animal sources. They represent either whole or parts of animals or their products and extracts. These include the medicinal leech (*Hirudo medicinalis*), cantharides (blistering beetles), lac or shellac (the resinous substance prepared from a secretion of the insect, Laccifer lacca), musk (the dried secretion from the preputial follicles of the musk deer, Moschus moschiferus), civet (the secretion obtained from the perineal follicles of civet cats (Viverra species), chalk (finely powdered whitish or grayish rock, which consists mainly of the shells of unicellular Foraminifera animals), cod-liver oil, halibut-liver oil, suet, lard, spermaceti, wool fat, gelatin, honey, beeswax, etc.

Some of the important drugs of animal origin are briefly described below in the form of monograph.

7.8.1 Hirudo medicinalis

Common Name: European medicinal leech (Eng.), Sangsue medicinal, Sangsue ofiicinale (French)

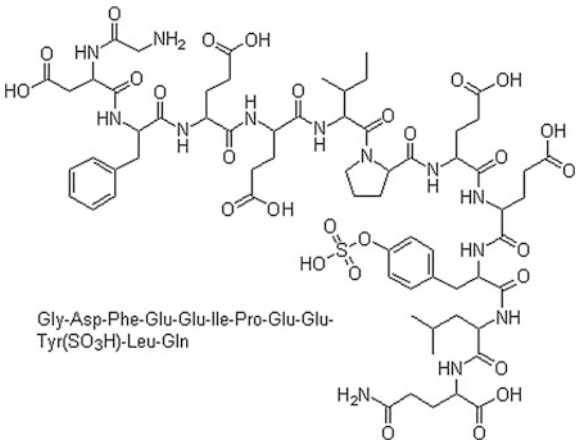
The European medicinal leech is one of the several species of leeches. A few other *Hirudo* species often used as medicinal leeches include *H. manillensis, H. orientalis*, *H. troctina*, *H. verbana*, *H. nipponia*. *Hirudinaria manillensis*, and *Macrobdella decora*.

Description: The general morphology of medicinal leeches is similar to most other leeches such as segmented and dorso-ventrally flattened. Adults can grow up to 20 cm in length; color may be green, brown, or greenish-brown with a darker tone on the dorsal side and a lighter ventral side and with a thin red stripe on dorsal side. The body is covered by a unilaminar epithelium composed of epithelial, sensory, and mucous glandular cells, and the epithelium is covered by a thin cuticle that is renewed every time the leech molts. Each leech has two suckers (anterior and posterior suckers). The anterior or oral sucker contains saw-like tripartite jaws and about 100 sharp teeth for incision, while the posterior (large disc-shaped and

non-perforated) sucker is used mainly for leverage (locomotion). The incision leaves an inverted Y sign mark inside of a circle. An adult may consume ~10 times their body weight in a single meal, with 5–15 ml being the average volume taken (1). They are hermaphrodites, reproduced by sexual mating; inseminated leeches lay their eggs during the spring and in summer, lay eggs in clutches of up to 50 near water (but not under) and in shaded and humid places. Leeches mainly feed on the blood of mammals and can survive for long periods without eating. The European medicinal leech can be used for bloodletting. However, related species are usually used for medical purposes and in life sciences as model organisms.

Distribution: The range of distribution extends over almost the whole of Europe and into Asia as far as Kazakhstan and Uzbekistan. The range extends through parts of Western and Southern Europe to the Ural Mountains and the countries bordering the northeastern Mediterranean (2). The medicinal leech is a blood-sucking aquatic animal. It lives in mostly stagnant (marshes, ponds) fresh water but can also be found in streams. The preferred habitat for this species is muddy freshwater pools and ditches with plentiful weed growth in temperate climates. Depending on their geographic origin, leeches have different pigmentations making it possible to differentiate between different varieties.

Chemical constituents: After piercing the skin, leeches secrete saliva containing about 60 different proteins (3), and many of them function as anesthetics, anticoagulants (hirudin—a peptide of ~65 amino acids), platelet aggregation inhibitors (apyrase, collagenase, and calin), vasodilators, and proteinase inhibitors (4, 5). Apyrase (EC 3.6.1.5) is a calcium-activated plasma membrane-bound enzyme that catalyzes the hydrolysis of ATP to yield AMP and inorganic phosphate. The salivary apyrases of leech as well as blood-feeding arthropods are nucleotide hydrolyzing enzymes that are implicated in the inhibition of host platelet aggregation. The leech salivary glands also secrete mucous to lubricate the jaws and to ensure hydration of the stored blood as well as protein to ensure diffusion, vasodilation, etc.



Name: [Try(SO3H)63]-Hirudin fragment 54-65; Synonyms: Gly-Asp-Phe-Glu-Glu-Ile-Pro-Glu-Glu-Tyr(SO3H)-Leu-Gln; Mol. formula: $C_{66}H_{93}O_{28}S$; Mol. wt. 1548.58; CAS registry number: 109528-49-6; Source: Sigma Aldrich.

www.sigmaaldrich.com/catalog/Lookup.do?N5=All&N3=mode+matchpartialmax&N1=S_ID&ST=RS&N25=0&F=PR&D7=0&N4=109528-49-6

Medicinal use: The medicinal leeches have historically been used for medicinal purposes, mainly to remove 'bad blood' from the diseased. They secrete saliva containing a wide variety of active substances which achieve a wide variety of therapeutic goals. Medicinal leech therapy used in microsurgery (6, 7) is useful to stimulate circulation to salvage skin grafts and other tissue threatened by postoperative venous congestion (6, 8), particularly in finger reattachment and reconstructive surgery of the ear, nose, lip, and eyelid (7, 9). Other clinical applications of medicinal leech therapy include varicose veins, muscle cramps, thrombophlebitis, and osteoarthritis, etc. (10). The therapeutic effect is not from the blood taken in the meal, but from the continued and steady bleeding from the wound left after the leech has detached, as well as the anesthetizing, anti-inflammatory, and vasodilating properties of the secreted leech saliva (1). The most common complication from leech treatment is prolonged bleeding, which can easily be treated, although allergic reactions and bacterial infections may also occur (1). In addition, leech saliva is found to contain powerful antibiotics and anesthetics which no doubt will prove useful in future medicinal practice (2).

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7.8.2 Cantharides

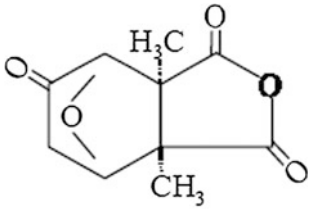
Synonyms: Spanish fly; Blistering fly; Blistering beetles.

Biological sources: Cantharides comprises of the dead and dried insects of Cantharis vesicatoria Linn., (Lyatta vesicatoria) belonging to the family Meloidae. Cantharides contains the colorless terpenoid furanocoumarin derivatives cantharidin (0.6–1%).

Geographical sources: Cantharides beetles are generally found in the Southern and Central Europe living on the plants belonging to the family Oleaceae and Caprifoliaceae. Large-scale collection of blistering beetles for commercial purpose takes place in Russian Federation, Italy, Spain, Sicily, and India (1, 2, 3).

Description: Color-brilliant green or bronze green; Odor—characteristic odor; size approximately 5 mm in width and 20 mm in length long (4, 5, 6, 7).

Chemical constituents: Cantharides secrete an important vesicating principle—cantharidin ($C_{10}H_{12}O_4$), an odorless, colorless terpenoid present in the soft portion of the many species of blister beetles. The beetles also contain resin, formic acid, uric acid, and fat (12–15%).



Cantharidin

The active agent cantharidin is also produced by some other insects like *Epicauta immaculate* (5).

Preparation: The fully developed insects, brilliant green in appearance with distinct metallic luster, are collected in the early morning on large spread cloth by vigorously shaking the branches of the host shrubs, sacrificed by either exposure to chloroform, sulfur dioxide, and ammonia vapor in closed chamber or dipping them into vinegar. The dead beetles are then dried at 40 °C. Active agent present about 0.2–0.7 mg per beetle.

Substituents/Adulterants: Cantharides beetles are mostly substituted by the dried Mylabris spp. (M. cichorii or M. pustulata) abundantly found in China and India. They contain 1–1.2% cantharidin.

Toxicity: Cantharidin is dangerously toxic, inhibiting the enzyme phosphatase 2A (PP2 or PP2A). It causes irritation, blistering, bleeding, discomfort, renal dysfunction, and even death (8, 9, 10, 11). Cantharidin poisoning includes blood in the urine, abdominal pain, and often prolonged erection (12).

Uses: As a blister agent, it is in a list of 'problem drugs' used by dermatologists (12) and emergency personnel (13). It can be applied in the clinic safely and effectively to treat warts and molluscum (14), as hair growth stimulant in hair oil and also as vesicant, rubrifacient, and counterirritant. Cantharidin was once used as an aphrodisiac (love powder, a deadly viagra of the past), but the extreme toxicity makes its use highly dangerous (15, 16). In Santeria, cantharides are used in incense (17).

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7.8.3 Cod-Liver Oil

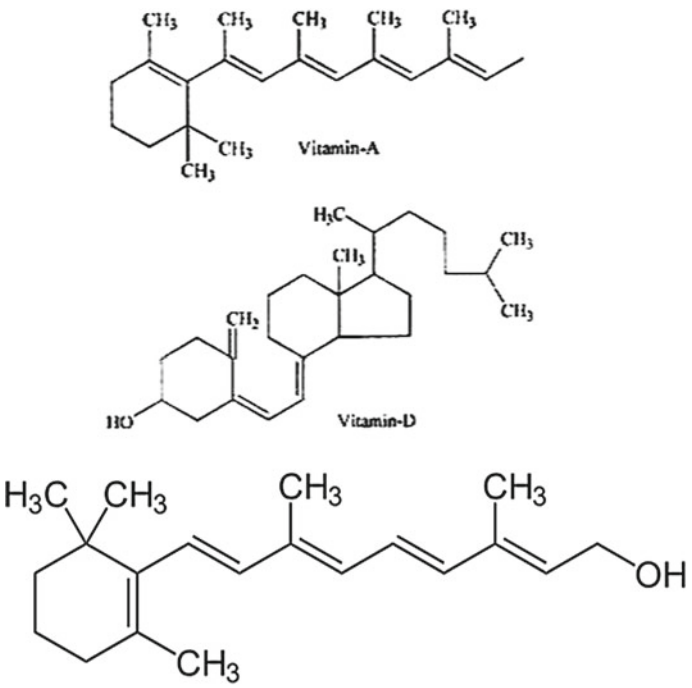
Synonyms: Oleum Morrhuae, Morrhua oil

Biological source: Cod-liver oil is obtained by extracting the fresh liver of the cod, *Gadus morrhua* Linn., and other species of Gadus (Family Gadidae)(1).

Geographical source: North coast of Norway, Newfoundland, Denmark, Germany, Scotland, and Iceland are the principal sources of the cod-liver oil.

Macroscopical and microscopical characters: Cod-liver oil is a pale yellow oily liquid with a fishy odor and a bland fishy taste. It is slightly soluble in alcohol, but miscible with chloroform, ether and light petroleum. The specific gravity of the oil varies from 0.922 to 0.929. It remains clear on standing for three hours

Chemical constituents: Though similar in composition with fish oil, cod-liver oil has higher concentrations of vitamins A and D. Cod-liver oil contains about 85 percent of glycerides of unsaturated fatty acids, cholesterol, vitamin A (000–35,000 IU/g), and vitamin D (65–150 IU/g). According to the US Department of Agriculture, a tablespoon (15 ml) of cod-liver oil contains 4080 μg of retinol (vitamin A) and 34 μg of vitamin D (2).



Structure of all-trans retinol

Uses: Cod-liver oil is used as a nutritional supplement and in the prevention, treatment, and cure of vitamin A and D deficiency diseases like rickets and xerophthalmia and also in treating tuberculosis. Rich in omega-3 fatty acids, cod-liver oil may be beneficial in secondary prophylaxis after a heart attack (3). Diets supplemented with cod-liver oil have also been demonstrated to have beneficial effects on psoriasis (4).

Dose: Per tablespoon (13.6 g), cod-liver oil contains 136% of the established daily tolerable upper intake level (UL) for preformed vitamin A (Retinol) (5).

Toxicity: Vitamin A accumulates in the liver and can reach harmful levels sufficient to cause hypervitaminosis A (6). A high intake of cod-liver oil by pregnant women is associated with a nearly fivefold increased risk of gestational hypertension (7).

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7.8.4 Honey

Synonyms

Mel, Clarified Honey, Strained Honey

Biological source

Honey is a saccharine secretion produced from the nectar of flowers and accumulated in the honeycomb by the Honeybee, Apis mellifera Linn (family Apidae).

Geographical source

Although honey is collected in many tropical countries of the world, the chief sources of commercial supply include California, Jamaica, Chile, and also Britain.

Macroscopical and microscopical characters

Honey is a viscous, translucent, sticky liquid, when fresh. It becomes partially crystalline and semisolid on keeping. Honey varies in color from nearly white to yellowish brown. It possesses an agreeable characteristic odor and a sweet characteristic taste. The specific gravity of honey is greater than one. It is soluble in water and alcohol.

Physical characters

Fresh honey is a supersaturated liquid, containing more sugar than the water. At room temperature, honey is a supercooled liquid in which the glucose will precipitate into solid granules. This forms a semisolid solution of precipitated glucose crystals in a solution of fructose and other ingredients.

Chemical constituents

Honey is a mixture of sugars and other carbohydrates, mainly fructose ($\sim$38%) and glucose ($\sim$32%), and the remaining sugars are maltose, sucrose, and other complex carbohydrates and 15–20% of water. It also contains small quantities of dextrin, volatile oil, wax, and pollen grains. Honey has a low content of fat, dietary fiber, and protein.

Uses

Natural medicines are often tried for many conditions based on tradition or belief, but not all of these uses are supported by scientific research. Honey is used as a nutrient (source of carbohydrate during malnutrition or vigorous exercise), a demulcent, and as a sweetening agent. Honey is used orally for cough, diabetes, hypercholesterolemia, asthma, allergic rhinitis, diarrhea, mucositis, and gastric ulcer associated with *Helicobacter pylori*. It is used orally for wound healing following tonsillectomy and also in the mouth to prevent mucositis associated with chemotherapy or radiotherapy and for gingivitis. Topically, honey is used for wound healing, burns, diabetic foot ulcers, and gangrene and for treating cataracts and postherpetic corneal opacities as we as for sunburn and to prevent surgical tumor implantation or catheter-related infections. Honey is used topically to treat symptoms of hemorrhoids and for herpes infections. In a nasal spray, honey is used for allergic rhinitis. Intravaginally, honey is used to improve fertility. Honey is used as a fragrance and a moisturizer in soaps and cosmetics.

Safety

Honey is generally safe (1), but may have various, potential adverse effects or interactions with excessive consumption, existing disease conditions, or drugs. Most microorganisms do not grow in honey (2); however, honey sometimes contains dormant endospores of the bacterium *Clostridium botulinum*, which can be dangerous to babies, as it may result in botulism (3).

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Chapter 8
Fibers, Surgical Dressings, and Bandages of Natural Origin

Abstract Plant fibers and the surgical dressings are valuable in medical and pharmaceutical practices. A dressing makes direct contact with the wound while a bandage is primarily used to hold a dressing in place. However, some organizations (e.g., the British pharmacopoeia) classify them as the same thing. Dressings are frequently used in first aid and nursing to promote healing and stop further tissue damage due to infection and mechanical hazards. An ideal wound dressing is to be sterile, breathable, and conducive for a moist healing environment. Modern dressings include gauze, films, gels, hydrogels, hydrocolloids, foams, alginates, polysaccharide pastes, granules, and beads. The quality of surgical dressings depends on the type of the fiber used to prepare the dressing. Plant fibers include epidermal trichomes (cotton), phloem or bast fibers (jute), and pericyclic fibers (flax, hemp), while fibers of animal origin include wool and silk. Artificial fiber of plant tissue origin is wood cellulose (rayon, cellulose wadding, alginate fibers, etc.) and synthetically prepared fibers (nylon and terylene) are also frequently used in wound management as surgical dressings.

Keywords Plant fibers · Surgical dressings · Bandage · Gauze · Gels · Colloids

8.1 Natural Fibers

Fibers are minute thread-like substances of natural or synthetic origin. They are composed of different types of polymer molecules. In pharmacognosy, natural fibers are described as elongated thick-walled cells with pointed ends, and their cell walls consist of cellulose and may or may not contain lignin. The natural fibers are derived from vegetable, animal, or mineral. The advantage of natural fibers is their continuous supply, easy and safe handling, low-cost, low density, high specific properties, non-abrasive, non-carcinogenic, and biodegradable property (Brouwer 2000; Peijs 2000; Chand 2006). Plant-derived fibers are grouped as phloem or bast (flax, jute, kenaf, hemp, ramie, and rattan), leaf (sansevieria, fique, banana, pineapple, agave, abaca, and sisal), fruit (oil palm, rice husk), seed (cotton, coir,

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linseed and kapok), and stem or stalk (Abaca, wheat, rice, barley, sugarcane, grass, bamboo, broom, elephant grass, ramie, roselle, sisal, and tree wood) fibers, and they are produced in huge quantity annually across the globe (John and Thomas 2008; Faruk et al. 2012). These fibers are composed principally of cellulose, with varying amounts of lignin and hemicelluloses (cellulose or lignocellulosic fibers) (Li et al. 2007; Taj et al. 2007). Vegetable fibers are usually stiffer but less tough than synthetic fibers, and these fibers are grown throughout the world but mostly in tropical and subtropical climates (Young 2004).

Animal fibers are comprised of proteins (collagen, keratin, and fibroin). Examples include sheep wool, goat hair (cashmere, mohair), alpaca hair, horse hair or hairs, silk (secreted by glands of insects during the preparation of cocoons), tendon or sinew, catgut (cord made from sheep, goat or cattle intestine walls), angora wool (hair of angora rabbit), fur (from fox, rabbit, mink, beavers, ermine, otters), and avian fiber (birds feathers and feather fiber). Fibers may be regenerated from carbohydrate materials (alginate yarn, artificial silk or rayon or regenerated cellulose), protein materials (aridil from groundnut protein, fibrolan from milk casein) or through chemical synthesis (nylon, terylene, orlon). Glass and asbestos belong to mineral fibers.

Apart from three natural sources (e.g., plant, animal, mineral), fibers used in surgical dressings are now synthesized artificially from various ingredients. The various groups of fibers may be conveniently summarized in Fig. 8.1.

Fibers are used in medical textiles (surgical, extracorporeal, healthcare and hygiene products, etc.) or medtech—an important, continuously expanding and growing field in technical textiles, for the production of a wide variety of woven, nonwoven, knitted forms of textile that are increasingly finding their way into a

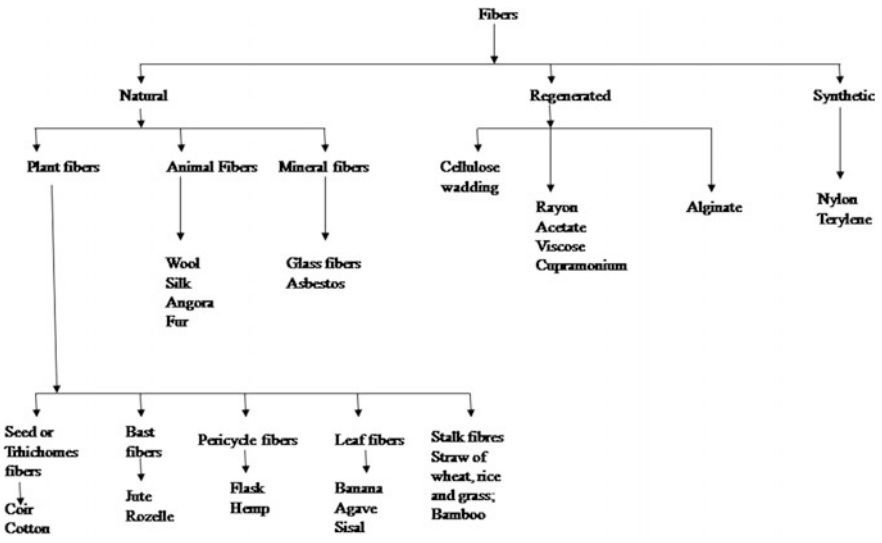

Fig. 8.1 Classification of fibers used in dressing

variety of surgical procedures. The medtech products are diverse, ranging from a single thread suture, surgical dressings, mask, surgical gauze, roller bandage, plastic bandage, wound care, absorbent cotton, incontinence pads, felts, apparels, spunlace, diapers, plasters, pressure garments, orthopedic belts, etc., to the complex composite structures for bone replacement and from the simple cleaning wipe to advanced barrier fabrics used in operating rooms, clinics, and hospitals (Akter et al. 2014). The medtech products may be segregated as non-implantable materials, which used for external applications on the body (wound care, bandages, plasters, pressure garments, orthopedic belts, etc.), and implantable materials, which are used in effecting repair to the body (wound closure or sutures) and replacement surgery (vascular grafts, artificial ligaments, etc.). Medical textile products are valuable in medical and pharmaceutical practices (Fig. 8.2).

Some of these natural, regenerated, and synthetic fibers used for surgical dressings are described in brief in the following pages in the form of Monographs.

8.1.1 Plant Fibers

Cotton

Synonyms: Raw cotton wool, absorbent cotton, surgical cotton

Biological Source: Cotton consists of the epidermal trichomes of the seeds of *Gossypium herbaceum* L. and other species of *Gossypium* of the family Malvaceae (Fig. 8.3).

Geographical Source: *Gossypium* species are cultivated for commercial production of cotton in the USA, West Indies, Peru, Brazil, India, China, and Egypt. Cotton plants are also now cultivated in Nigeria and Bangladesh.

Preparation of Raw Cotton: Bolls of cotton are collected from the ripe and dehisced fruits of *Gossypium*. The trichomes are separated from the seeds by a ginning process using a machine called gin, in which the trichomes are drawn through a narrow space. The masses of these separated trichomes constitute raw

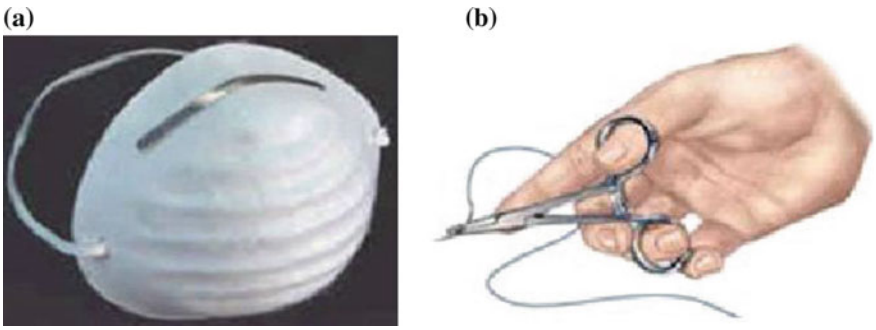

Fig. 8.2 **a** Surgical mask, **b** surgical suture (*Source* Akter et al. 2014)

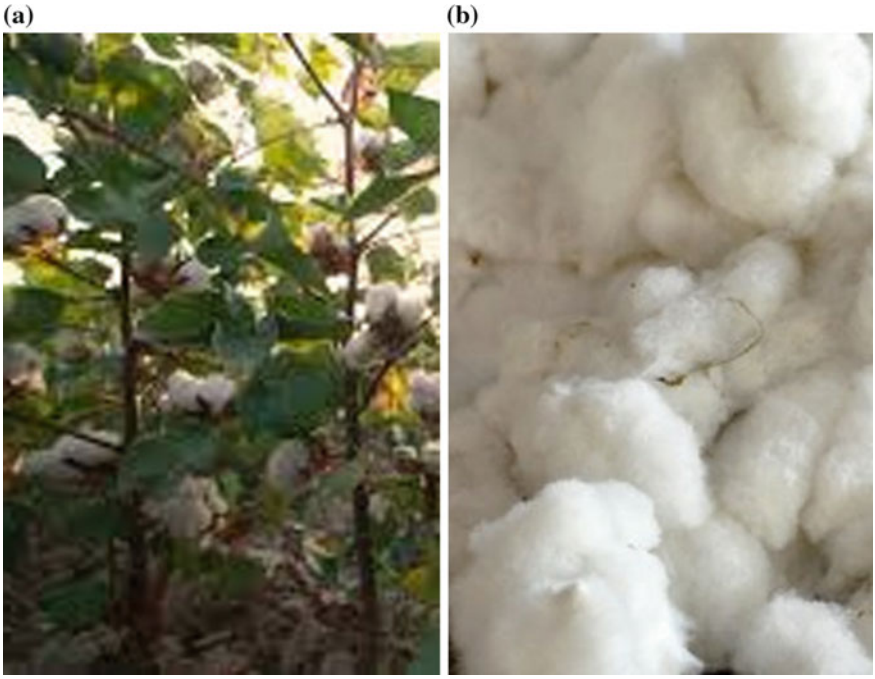

Fig. 8.3 **a** Cotton plant with split boll, **b** extracted fiber

cotton. Raw cotton thus prepared contains impurities, chiefly coloring matter, and about 0.6% of wax and oil, which form a thin film-around the fibers and render them non-absorbent. Raw cotton is then variously treated, combed, and spinned to convert it to yam or thread, which are woven to make fabrics and cloths.

Preparation of Absorbent Cotton Wool: Absorbent cotton wool is prepared from the various cotton wastes obtained during the processing of raw cotton for making yarns. The wastes are loosened and then boiled for 10–15 h under a pressure of about 30 lbs in a dilute solution of caustic soda and soda ash. This treatment removes the fatty cuticle and renders the trichomes absorbent. The boiled material is then washed thoroughly with water, bleached with dilute sodium hypochlorite solution, and treated with very dilute hydrochloric acid. The bleached mass of fibers is then dried, loosened, scutched, and carded by using appropriate machines. The resultant product is a thin continuous film of absorbent cotton wool. Several such films are superimposed on one another and rolled.

Macroscopical and Microscopical Characters: Cotton wool is a loose mass of thin filaments, soft to touch, and white in color. Absorbent cotton wool is whiter than the raw cotton, which has a brownish tint. When pulled apart, a wad of cotton wool separates with resistance, and in a dragging fashion, forming a thin film of fibers being finally separated. When placed on the surface of water, raw cotton floats while absorbent cotton rapidly sinks. The cotton trichomes are tubular,

flattened, and twisted with large lumen. The apex is rounded. The cellulose wall of the raw cotton fiber is covered with a waxy cuticle. When treated with ammoniacal copper oxide solution (CUOXAM), raw cotton fibers dissolve with ballooning, while those of absorbent cotton dissolves with uniform swelling. Cotton dissolves in 80% cold sulfuric acid.

Different commercial varieties of cotton can be distinguished by the length of staple of the trichomes. The staples of the important varieties of cotton are as follows; Sea Island, up to 54.5 mm; Egyptian, 31–38 mm; Peruvian and Brazilian, 29–30 mm, and Indian 21.4–29.2 mm.

Constituents: Raw cotton contains about 90% of cellulose and small amounts of wax, fat, and remains of protoplasm and ash. Absorbent cotton is almost pure cellulose.

Uses: Cotton is used as the chief material for many surgical dressings. It is also used as a filtering medium and an insulating material.

Jute

Synonym: Gunny.

Biological Source: Strands of phloem fibers of the stem bark of *Corchorus olitorius* L. and *Corchorus capsularis* L. (Family Tiliaceae) constitute jute. Jute is one of the longest and most used natural fiber, next to cotton in amount produced (Fig. 8.3).

Geographical Source: Jute is extensively cultivated as a cash crop in Bangladesh, which supplies more than 95% of the world's requirement of this important fiber. It is also cultivated in small quantities in some parts of India (Fig. 8.4).

Preparation of Jute Fiber: Jute plants are normally straight and unbranched. They are cut from the base when the plants are in flower, tied into small bundles, stacked, and soaked in stagnant water for about 3 weeks for retting. The stacks are covered with straw or water hyacinths to keep them wet and to protect from direct sunlight. When the stem bark is well-macerated by the retting process, the strands of the phloem fibers are separated manually from the wood and washed free from the surrounding softer tissues and other dirt thoroughly in clean water. The fibers are then dried in direct sunlight and made into small bundles. Jute fiber is exported in bales made by hydraulic pressure.

Macroscopical and Microscopical Characters: The strands of jute are pale buff or silvery gray in color, 1–3 mm long and about 30–140 μm in diameter, somewhat coarse in texture. They have great tensile strength. The individual fibers vary from 0.8 to 5.0 mm in length and 10 to 25 μm in diameter, with a quite smooth surface. The lumen is not uniform throughout the length of the fiber owing to variation in the thickness of the walls. The ends of the fibers are rounded and blunt. In transverse sections, the cells appear polygonal in outline with a rounded lumen which varies considerably in size.

Jute fibers do not swell in CUOXAM. They are insoluble in 80% sulfuric acid and stain red with phloroglucinol and hydrochloric acid.

Fig. 8.4 **a** Jute plant with long stem, **b** bundle of extracted fiber

Constituents: Jute fibers are composed of 53% cellulose and 22% hemicelluloses and contain 11% of lignin, 0.1% of fats and waxes, and 1% of ash.

Uses: In pharmacy, jute is used for the manufacture of medicated tows, for padding splints, as a filtering or straining medium, and for soaking fluids. Other industrial uses of jute include the manufacture of ropes, gunny bags, carpet backings, and yarns for some fabrics.

Flax

Synonym: Tishi, Linseed.

Flax is one of the oldest fiber crops in the world. It was used by the ancient Egyptians, Romans, Greeks, and Hebrews for food, clothing, and medicine.

Biological Source: Flax consists of the strands of pericyclic fiber of the stem of *Linum usitatissimum* L., a cultivated plant of the family Linaceae (Fig. 8.5).

Fig. 8.5 **a** Flax plant with flower and long stem, **b** soft lustrous bundles of fiber

Geographical Source: *Linum usitatissimum* is cultivated in many countries including Bangladesh as an oil-seed plant, but always as a source of fiber. Flax is prepared commercially in Russia, Northern Ireland, USA, and Argentina.

Preparation of Flax: The plants are uprooted by hand just about the time of ripening of the fruits, tied in sheaves, and left to dry in the field. The dried plants then undergo a rippling process to remove the capsules, after which the sterns are tied in bundles and subjected to a retting process similar to that of jute. When retting is complete, the stalks are dried in the sun, broken into pieces in a mill and

the pieces of the xylem tissues removed by the teeth of a scutcher. The residual bark from the stem is then mechanically combed to make the fibers parallel,

Macroscopical and Microscopical Characters: The strands of flax fibers have more tensile strength than cotton. They are about 50 cm in length, the individual fibers vary in length from 12 to 30 nm; have very thick walls, uniform narrow lumen and finely pointed ends. Fine, obliquely transverse markings are present on the fibers. They are also finely striated longitudinally.

Constituents: Flax is made up of pecto-cellulose.

Uses: Flax is used as a filtering medium for some preparations. It is rarely used in the manufacture of lints.

8.1.2 Animal Fibers

Wool

Synonyms: Animal wool, sheep's wool.

Biological Source: Wool consists of the hairs of the fleece of sheep, *Ovis aries* L., family Bovidae.

Geographical Source: Wool is produced and exported by the USA, Australia, Argentina, Russia, and the British Isles (Fig. 8.6).

Preparation of Wool: The hairs are cut from the sheep at appropriate intervals and dirts removed by beating on a sieve screen. The dirt-free hairs are then thoroughly cleansed by washing with soap and sodium carbonate. The wool is then bleached with sulfur dioxide or hydrogen peroxide, thoroughly washed and dried by hot air on wire netting.

Macroscopical and Microscopical Characters: Wool occurs as a loose, soft mass of elastic lustrous curly hairs. When pulled, a wad of wool separates out with considerable resistance due to the clinging nature of the hairs. The individual hairs are subcylindrical, more or less curved, 2–50 cm in length, 5–100 μm in diameter. They are covered with imbricated flattened epithelial scales. A darker colored narrow band is present along the central axis of the hairs. When treated with CUOXAM, the fibers do not produce swellings, but stain blue. They are insoluble in 80% sulfuric acid,

Constituents: Wool fibers are composed almost entirely of the protein keratin, which contains C, H, O, N, and S.

Uses: Wool is used in the manufacture of dressings such as flannel, domette, and crepe bandages. Wool fibers and their yarns are of immense commercial value for their use in the textile industries for manufacturing warm fabrics.

Silk

Synonym: Rashom.

Biological Source: Silk consists of a fiber prepared from the filaments of the cocoons spun by the larvae of *Bombyx mori* L. (Family Bombycidae), the mulberry

Fig. 8.6 **a** Sheep, *Ovis aries*, **b** extracted soft lustrous wool

silkworm, and those of other species of Bombyx and of various species of *Antheraea* (Family Saturniidae)

Geographical Source: Silk is cultivated in Japan, China, France, and Italy. It is also cultivated in small quantities in Bangladesh and India (Fig. 8.7).

Preparation of Silk: The cocoons, a covering of filaments produced by the larvae of the silkworm around themselves before passing to their pupal stage, are collected immediately after the larvae reach the pupal stage. They are then baked or steamed to kill the pupae. The cocoons are then placed in hot water to soften and to remove partly the natural gum of the silk filaments. The ends of the filaments from two to six cocoons are then caught up and up winded. A number of these are twisted together to form a single thread of raw silk. This raw silk is made up into hanks for processing into fabrics.

Macroscopical and Microscopical Characters: Silk consists of very fine, soft, smooth, and solid threads, usually yellow in color. The threads possess considerable tensile strength. Under the microscope, silk appears as cylindrical or slightly flattened, structureless solid threads, 5–25 μm in diameter. It is easily soluble in CUOXAM, 66% cold sulfuric acid and concentrated hydrochloric acid.

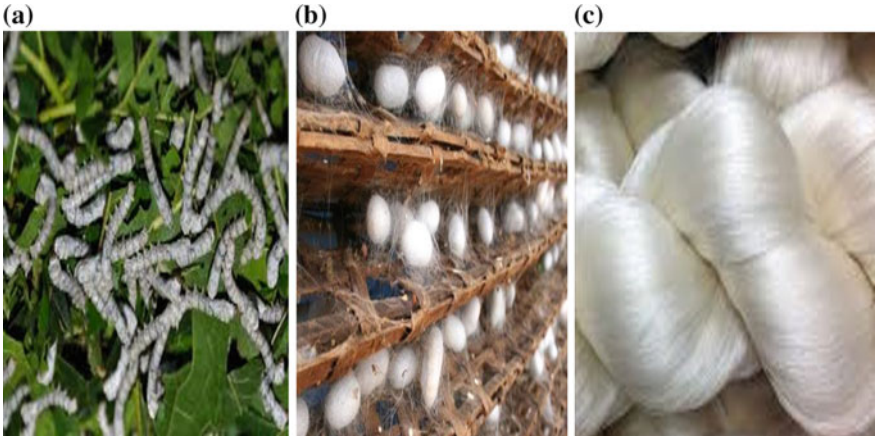

Fig. 8.7 **a** Silk worm, Sheep, **b** cocoon, **c** soft lustrous bundle of silk

Constituents: The mass of the silk fiber is made up of the protein fibroin, coated externally by another protein sericin or silk gum, which cements the fibers together. The proteins of silk do not contain sulfur.

Uses: The pharmaceutical uses of silk include the manufacture of ligatures, oiled silk, and some sieves.

8.1.3 Mineral Fibers

Glass Fibers

The fibers consist of sand, mixed with oxides of aluminum, calcium, boron, and magnesium. They are unaffected by all usual reagents used in identification of fibers.

Asbestos

It consists of mainly hydrated magnesium silicates.

Uses: It is used in the preparation of a filtering medium and for bacterial fibers.

8.2 Asbestos

8.2.1 Regenerated Fibers

Cellulose Wadding

Synonyms: Wool cellulose, chemical wood pulp.

Biological Source: Cellulose wadding is prepared from bleached sulfite wood pulp obtained from the wood of various conifers belonging to the family Pinaceae.

Geographical Source: Supplies of cellulose wadding come chiefly from the USA, Canada, and Germany.

Macroscopical and Microscopical Characters: The beaten wood pulp is strained through the wire of a machine, and thus, a fine web of fibers is left on top of the wire. This web after being dried and crepped gives a thin, soft, absorbent sheet. About 30 of these sheets laid together make cellulose wadding. Thus, it occurs as a felted sheet, about 1 cm thick, 1000 square centimeter of which weighs about 4.7 g. It is almost white in color as cotton, but harsher in texture. It breaks quickly when pulled (distinction from cotton wool). It is very absorbent and sinks in water more rapidly than cotton wool.

Characteristic wood elements are present in the fibers of cellulose wading. These elements are mainly tracheids with bordered pits and characteristic medullary ray cells. Cellulose wadding is soluble in 60% cold sulfuric acid and CUOXAM.

Constituents: Cellulose wadding consists almost entirely of pure cellulose.

Uses: Uses of cellulose wadding are similar to those of absorbent cotton wool. For certain purposes, it is preferred to absorbent cotton wool. For certain purposes, it is preferred to absorbent cotton wool because of its superior absorbent property and the readiness with which it disintegrates.

Rayon

Synonyms: Regenerated cellulose, artificial silk.

Biological Source: Rayons are prepared from the polysaccharide cellulose molecules derived from wood pulps by maceration and treatment with various chemical substances. Depending on the means used to bring the cellulose into solution to prepare the rayon fibers, Rayons are variously named such as acetate rayon, viscose rayon, cuprammonium rayon, nitrate rayon. Out of these, viscose rayon is mainly used for surgical dressing purposes.

Macroscopical and Microscopical Characters: Viscose rayon occurs in fibers, which are white and highly lustrous. Its tensile strength is much less than that of cotton. The fibers are solid and transparent and have a diameter ranging from 15 to 25 μm their surface is finely grooved by longitudinal lines. In transverse sections, they show an irregularly crenate margin.

Viscose rayon gives cellulose test with N/50 iodine solution and 80% sulfuric acid (blue color). It is soluble in CUOXAM and 60% cold sulfuric acid, but insoluble in 5% boiling potassium hydroxide solution.

Constituents: Viscose rayon is also composed almost entirely of cellulose. It also contains about 0.03% of sulfur and yields about 0.2–0.3% of ash.

Uses: Lint, gauze, nets, and other surgical dressings are made from viscose rayon.

Alginate Fibers

Synonym: Calcium alginate fibers.

Source and Preparation: Alginate fibers of surgical dressings are represented by the calcium alginate fibers, which are prepared from solutions of sodium alginate and calcium chloride. A spinning process similar to that for viscose rayon is used

for the preparation of these fibers. Calcium alginate fibers are also reduced to a staple for processing them to a wool or fabric such as viscose rayon or cotton.

Macroscopical and Microscopical Characters: Calcium alginate fibers are cream-colored lustrous fibers. Under the microscope, they appear as longitudinally finely grooved solid rods similar to those of viscose rayon. They are harsh in texture, colorless, and tasteless. Calcium alginate fibers swell and dissolve in ammoniacal copper nitrate, but are insoluble in 60% cold sulfuric acid, 5% boiling potassium hydroxide solution, and warm hydrochloric acid.

Uses: Calcium alginate fibers are used to prepare gauzes for absorbable hemostatic dressings and bacteriological swabs.

8.2.2 Synthetic Fibers

Nylon

Source: Nylon is a synthetic fiber, chemically synthesized by polymerization from long-chain adipic acid and hexamethylenediamine. The polycondensation product in molten condition is pumped through a spinning machine, and the resultant filaments are cold-drawn to increase their length.

8.3 Surgical Dressings

A dressing is an adjunct used for application to a wound to promote healing and/or protect the exposed tissues against microbial infections and other natural hazards. A dressing is designed to be in direct contact with the wound, which makes it different from a bandage, which is primarily used to hold a dressing in place. Some organizations (e.g., the British pharmacopoeia) classify them as the same thing and the terms are used interchangeably by some people. Historically, a dressing was usually a piece of cloth material, but the use of cobwebs, dung, leaves, and honey has also been described. Modern dressings, on the other hand, include gauze, films, gels, hydrogels, hydrocolloids, foams, alginates, polysaccharide pastes, granules, and beads. Many gauze dressings have a layer of nonstick film over the absorbent gauze to prevent the wound from adhering to the dressing. The success of wound management largely depends on the quality of the dressings used. Dressings are frequently used in first aid and nursing. A surgical dressing aid heals and stops further tissue damage.

Although all purposes of dressing are focused toward promoting recovery and preventing further harm from the wound, a dressing can have a number of purposes, depending on the type, severity, and position of the wound, e.g., (1) stem bleeding (help to seal the wound to expedite the clotting process); (2) absorb exudate (soak up blood, plasma, and other fluids exuded from the wound); (3) ease pain (pain relieving effect); (4) debride the wound (remove slough and foreign objects from

the wound); (5) protection from infection (defend the wound against germs and mechanical damage); (6) promote healing (contribute to recovery via granulation and epithelialization); (7) aquacel hydrofiber (control the moisture content of burns); (8) occlusive dressings (increase the rate of absorption of certain topical medications into the skin); (9) maintain optimum pH and temperature to encourage healing; (10) reduce psychological stress (obscure a healing wound from the view of others), etc. An ideal wound dressing is one that is sterile, breathable, and conducive to a moist healing environment.

The quality of surgical dressings depends on the type of the fiber used to prepare the dressing. Fibers are used for dressing purposes both in their normal forms and in woven or fabric forms. Fibers that are useful in wound management and healing include both natural (cotton, jute, flax, and hemp of plant origin; silk and wool of animal origin; asbestos and glass wool of mineral origin) and artificial or synthetic (regenerated rayon, nylon) fibers (Fig. 8.1). Natural fibers may be of plant or animal origin. Plant fibers include epidermal trichomes including cotton, and other fibrous tissues of plants such as phloem or bast fibers (jute, roselle) and pericyclic fibers (flax, hemp). Fibers of animal origin are derived from some animal products such as silk and wool. Artificial fibers, prepared by processing or regenerating some tissue elements of plants such as wood cellulose (e.g., rayon, cellulose wadding, alginate fibers), are also frequently used in wound management and surgical dressings. Some synthetically prepared fibers, such as nylon and terylene, have also been used for dressing wounds and burns.

Dressing aids to wound healing and wound is a disruption in the continuity of the epithelial lining of the skin or mucosa due to physical or thermal damage, accident or surgical injury. Dressing is designed to be in contact with the wound and bandage holds the dressing in place. Once wet-to-dry dressings were used extensively, then came the Linen strips (soaked in oil or grease covered with plasters), the Mesopotamian used clay tablets for the treatment of wounds after cleaning wounds with water or milk prior to dressing with honey or resin, Hippocrates used wine or vinegar for cleaning the wounds with honey and wool (boiled in water or wine) as a bandage, oil and wine as further treatment. A major breakthrough came in the nineteenth century with the introduction of antiseptic technique and modern wound dressing began in twentieth century.

Wound healing is a dynamic multi phase process of tissue regeneration (e.g., coagulation and hemostasis phase, inflammatory phase, proliferation period, and maturation phase) which requires suitable environment to promote healing process. It requires suitable dressing material that provides congenial atmosphere for rapid wound healing (e.g., moist environment, epidermal migration, enhanced angiogenesis and connective tissue synthesis, gas exchange between wounded tissue and environment, appropriate tissue temperature to improve the blood flow to the wound bed and enhances epidermal migration, protection against bacterial infection, non-adherent to the wound, debridement action to enhance leukocytes migration and support the accumulation of enzyme, and be sterile, non-toxic and non-allergic). When the wound is closed with dressing they are continuously exposed to proteinases, chemotactic, complement and growth factors, but they are

lost in the exposed wound, and only during late twentieth century, use of occlusive dressing began to protect by providing moist environment to wound. These dressings help in faster re-epithelialization, collagen synthesis, promotes angiogenesis by creating hypoxia to the wound bed and decreases wound bed pH to minimize wound infection. Once it was firmly believed that wounds healed more quickly under dry and uncovered conditions.

Traditional wound dressing products include gauze, lint, plasters, bandages (natural or synthetic), and cotton wool (dry products used for primary or secondary dressings). Gauze dressings (woven and nonwoven fibers of cotton, rayon, polyesters) provide protection against bacterial infection and require frequent changing to protect from maceration of healthy tissues.

Bandages of natural cotton wool and cellulose or synthetic materials (polyamide materials) perform different functions (e.g., cotton bandages are used for retention of light dressings, high compression bandages and short stretch compression bandages provide sustained compression in case of venous ulcers). Tulle dressings (e.g., Bactigras, Jelonet, Paratulle) are impregnated dressings with paraffin and suitable for superficial clean wound. Traditional dressings are cost effective and indicated for the clean and dry wounds with mild exudates levels or as secondary dressings. Traditional dressings are dry but become moistened (due to excessive wound drainage) and adherent to the wound making it painful when removing. The dry traditional dressings have now been replaced by modern dressings that provide moist environment to the wound.

Modern wound dressings, not just a cover, facilitate the function of the wound (protect dehydration and promote healing). Modern wound dressings are usually based on synthetic polymers and are classified as passive (non-occlusive), interactive (semi-occlusive or occlusive) and bioactive products. Passive products include gauze and tulle dressings while interactive dressings are available in the forms of films, foam, hydrogel, and hydrocolloids. Since 1990, various synthetic products are available for wound dressings, e.g., hydrogels, hydrocolloids, alginates, synthetic foam dressing, silicone meshes, tissue adhesives, vapor-permeable adhesive films, and silver or collagen (structural protein) containing dressing (biological dressings).

8.3.1 Hydrocolloid Dressing

Hydrocolloid dressings are among the most widely used interactive dressings and are consist of two layers, inner colloidal layer and outer water- impermeable layer. These dressings are made up of the combination of gel forming agents (carboxymethylcellulose, gelatin, and pectin) with other materials such as elastomers and adhesives. Hydrocolloids are permeable to water vapor, impermeable to bacteria, possess the debridement and wound exudates absorption properties. They are used on light to moderately exudating wounds (e.g., pressure sores, minor burn wounds, traumatic wounds). These dressings are also recommended for pediatric

wound care management, as they do not cause pain on removal. Hydrocolloids with wound exudate form gels and provide moist environment that helps in protection of granulation tissue but they are not indicated for neuropathic ulcers or highly exudating wounds. So, they are mostly used as secondary dressings.

8.3.2 Hydrogel Dressing

Hydrogels are insoluble hydrophilic materials made from synthetic polymers such as poly (methacrylates) and polyvinyl pyrrolidine. The high water content of hydrogels (70–90%) helps granulation tissues and epithelium in a moist environment. Soft elastic property of hydrogels provides easy application and removal after wound is healed without any damage. Temperature of cutaneous wounds is decreased by hydrogels providing soothing and cooling effect. Hydrogels are used for dry chronic wounds, necrotic wounds, pressure ulcers and burn wounds. Hydrogel dressings are non-irritant and non-reactive with biological tissue and permeable to metabolites. Difficulties of hydrogel dressings are exudate accumulation leads to maceration and bacterial proliferation that produces foul smell in wounds. Low mechanical strength of hydrogels is also a drawback. Examples of hydrogels include Intrasite, Nu-gel, Aquaform polymers, sheet dressings, impregnated gauze, water-based gels.

8.3.3 Alginate Dressing

Alginate dressings are made from the sodium and calcium salts comprising mannuronic and guluronic acid units. Absorbent and biodegradable alginates are derived from seaweed. Absorption capability is achieved by strong hydrophilic gel formation, which limits wound exudates and minimizes bacterial contamination, but may inhibit keratinocytes migration. On application of alginate dressings to the wound, ions present in the alginate are exchanged with blood to form a protective film. Alginate dressings are suitable for moderate to heavy drainage wounds and not suggested for dry wound, third-degree burn wound and severe wounds with exposed bone. Also these dressings require secondary dressings because it could dehydrate the wound which delays healing. Sorbsan, Kaltostat, and Algisite are some examples of commercially available alginate dressings.

8.3.4 Collagen Dressing

The various limitations of synthetic dressings led researchers to the development of a good functional collagen based biological dressings. Collagens are the most

abundant and ubiquitous structural proteins in vertebrates. Collagens provide mechanical support to the connective tissue and also form an essential substrate for cellular adhesion and migration and so collagen is considered to be an important factor in the regenerative process. It is hemostatic, has low antigenicity, and supports cellular growth. Collagen is a major structural protein and active in natural healing process. Collagen initiates fibroblast formation and accelerates endothelial migration upon contact with wound tissue. Hyaluronic acid (HA) is a glycosaminoglycan component of extra cellular matrix (ECM) with unique biological and physicochemical features. Similar to collagen, HA also biocompatible, biodegradable and lack immunogenicity naturally. Chitosan promotes the formation of granulation tissue during the proliferative stage of wound healing. When compared to other dressings, biological dressings are reported to be more superior to other types of dressings.

The last type of modern wound dressing is bioactive dressings and is produced from biomaterials which play an important role in healing process. These dressings are known for their biocompatibility, biodegradability and non-toxic nature and are derived generally from natural tissues or artificial sources such as collagen, hyaluronic acid, chitosan, alginate, and elastin. Polymers of these materials are used alone or in combination depending on the nature and type of wound. Biological dressings are sometimes incorporated with growth factors and antimicrobials to enhance wound healing process.

8.3.5 Composite Dressing

Composite or combination dressings are versatile and convenient for both partial and full thickness wounds. A composite dressing has multiple layers (in most cases three layers) and each layer is physiologically distinct. The outer most layer protects the wound from infection, middle layer usually composed of absorptive material which maintains moisture environment and assists autolytic debridement, bottom layer composed of non-adherent material which prevents from sticking to young granulating tissues. Composite dressings may also include an adhesive border of nonwoven fabric tape or transparent film. They can function as either a primary or a secondary dressing on a wide variety of wounds and may be used with topical medications. They are less flexible and are more expensive.

8.3.6 Standard Dressing of BPC

Standard Dressings

This group of surgical dressings includes some standardized compound dressings described in the British Pharmaceutical Codex (BPC) and other official publications. These dressings are prepared ready for use and consist of a pad of medicated

cotton wool, gauze or lint stitched to an open-wove bandage at certain distance from one end. The longer end of the bandage is rolled and placed inside the pad and the other end is wound round the rolled pad. The complete dressing is wrapped in impermeable paper and sterilized. However, in case of standard elastic adhesive dressings, the pad is fixed to a base of elastic adhesive cotton fabric, and no bandage is required. The standard dressings of BPC are numbered 1–15 and variously named as follows:

Standard Dressing No. 1: This dressing is also known as double cyanide dressing and consists of separate pieces of double cyanide gauze, absorbent cotton wool and an open-wove bandage, all wrapped together and sterilized.

Standard Dressing No. 2: This Standard dressing, also known as fomentation dressing, consists of separate pieces of boric acid lint, absorbent cotton wool and an open-wove bandage, all wrapped together and sterilized.

Standard Dressing Nos. 3. 4, 5 and 6: They are collectively known as elastic adhesive wound dressings and differ from each other only in size. All of them consist of a pad fixed centrally to a flesh colored elastic cotton fabric with an adhesive margin all round. The pad is made up of a strip of lint enclosed in one ply Muslin bandage; both medicated with about 5% of boric acid and tinted pink with a dye.

Standard Dressing No. 7: This is a plain lint finger dressing, which consists of a sterile unmedicated open-ended tubular bandage. This dressing is used as a wound dressing for fingers and toes.

Standard Dressing Nos. 8 and 9: These are also sterile plain lint dressings, which consist of an unmedicated pad of absorbent cotton wool faced with a rectangular piece of lint attached lengthwise to an open-wove bandage. These dressings differing only in their sizes are used as wound dressings for hands and feet.

Standard Dressing No. 10: It is also known as medicated lint finger dressing. It is a medicated (with Euflavine) version of the standard dressing No. 7 and is used for the treatment of mild burns of fingers and toes.

Standard Dressing Nos. 11 and 12: They are popularly known as bum dressings. These dressing are the medicated (with Euflavine) versions of Plain lint dressings (standard dressing Nos. 8 and 9). They are used for the treatment of mild bums of hands, feet, and larger areas.

Standard Dressing Nos. 13, 14 and 15: These unmedicated dressings are commonly referred to as plain wound dressings and are prepared in three different sizes: small (13) medium (14) and large (15). They consist of a pad of absorbent cotton wool, enclosed in absorbent gauze and attached to an open-wove bandage. They are sterile dressings. These are used as protective and absorbent dressings for wounds.

Standard Dressing No 16 or Eye pad with Bandage: It consists of a 150 mm by 75 mm oval-shaped pad of cotton wool covered on both sides with Muslin. The pad is longitudinally attached to a piece of open-wove bandage and is sterilized. The dressing is used as protective covering of the eye.

8.4 Bandage

A bandage is a piece of material used to support a medical dressing, splint, etc. to hold a medical dressing in place and to restrict the movement of a part of the body. In American English, the word 'bandage' is often used to indicate a small gauze dressing attached to an adhesive bandage. Bandages hold a splint in position or immobilize an injured part of the body to prevent further injury and to facilitate healing. When used with a dressing, the dressing is applied directly on a wound and a bandage used to hold it in place. In addition, bandages may be used to stop the flow of blood (tight bandage) to an extremity (in case of heavily bleeding of arms or legs) and also to provide a safeguard against contamination. Elastic bandages are used to reduce swelling or to provide support to a sprained ankle are used without dressings. Bandages are available in a wide range of types, from generic cloth strips to specialized shaped bandages designed for a specific limb or part of the body. Bandages can often be improvised as the situation demands, using clothing, blankets or other material.

Bandages are continuous length of fabrics and contain no joints. Their edges are evenly cut, parallel to the warp threads. They are reasonably free from loose threads. Bandages are chiefly made from plain or treated cotton cloths, but some are also made from wool and some other bandages are made from fabrics containing a mixture of both cotton and wool of natural origin.

Bandages may be classified into four categories according to the type of fabrics from which they are made (Fig. 8.8).

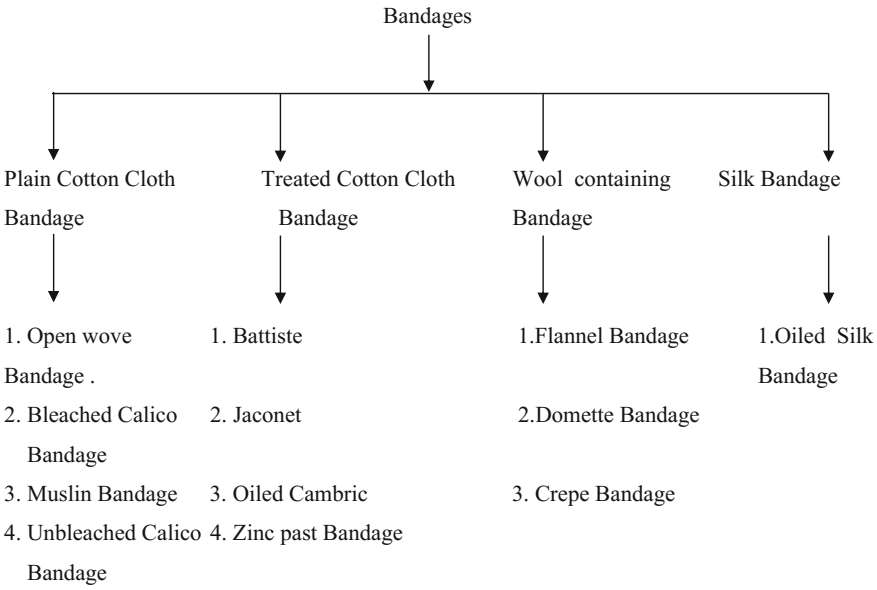

Fig. 8.8 Classification of bandages on the basis of the type of fabrics

Plain Cotton Cloth Bandages

Open-Wove Bandage: This is a white bandage, which contains not less than 43 threads per inch in the warp and 27 in the weft. A 2 in ×4 yd open-wove bandage weighs not less than 12.96 g.

Bleached Calico Bandage: This is a very closely woven white bandage containing 67 threads per inch in the warp and 58 in the weft. A 2 in. ×4 yd bleached calico bandage weighs not less than 13.6 g

Muslin Bandage: This is a bleached bandage of fine threads. It may be regarded as a very closely woven absorbent gauze. It contains 48 threads per inch in the warp and 30 in the weft. 1 ft^2 of this bandage weighs not less than 3.25 g.

Unbleached Calico Bandage: This bandage contains 65 threads per inch in the warp and 60 in the weft. A piece of 2 in ×4 yd size of this bandage weighs not less than 16.2 g

Treated Cotton Cloth Bandages

These bandages are made of cotton fabrics, which are variously treated to render them waterproof on one or both sides. They may be medicated or unmedicated. They include the following:

Battiste: It is a bleached fabric, rendered impervious to water by proofing its both sides with rubber.

Jaconet: This is also bleached fabric like Battiste, but it is water proofed only on one side with rubber.

Oiled Cambric: This is a yellow colored cambric, rendered water proof by treatment inch in the warp and 28 in the weft. A 2 in ×6 yd flannel bandage weighs not less than 58.3 g.

Domette Bandage: It is made up of a mixed fabric, which contains cotton threads in the warp (not less than 40 per inch) and wool threads in the weft (not less than 22 per inch). A 2 in ×6 yd of this bandage weighs not less than 28.5 g.

Crepe Bandage: This bandage also consists of a mixed fabric, wool and cotton threads in the warp and only cotton threads in the weft. However, it contains not less than 33.3% of wool, which is responsible for its crepe nature. When fully extended, the bandage must measure not less than twice the length of its upstretched condition. It must return to not of the fully extended length after being held, fully stretched for 1 min.

Silk Bandage

Silk fabrics are used to prepare some special type of surgical dressings. One of them is the following:

Oiled Silk Bandage: This bandage consists of a pure silk fabric having 120 threads per inch in the warp and 85 in the weft. The bandage is rendered completely waterproof by treating the fabric with a suitable drying oil or an oil modified synthetic resin. It may be colored green with a suitable dye.

Lints

Lints are medicated or unmedicated absorbent surgical dressings. They are made of plain wove absorbent cotton fabrics. The threads in the warp of the lint fabrics are

raised to form a nap. They contain not less than 39 threads per inch in the warp and 24 in the weft. About 230–250 sq. inch superficial area of the lints should weigh about 28.35 g.

The Following Medicated Lints Are Available

Boric Acid Lint: This contains 3–7% of boric acid, and is tinted with a suitable dye.

Euflavine Lint: This type of lint contains about 0.1% of euflavine.

Plasters

Plasters are a kind of adhesive bandage made from bleached cotton fabrics. An adhesive compound is spread on one side of the bandage to make it stick to the skin. Plasters may be either medicated or unmedicated. Some common plasters include the following:

Rubber Adhesive Plaster: This is a bleached cotton fabric of prescribed standard, prepared with an adhesive compound spread on one side and waterproofed with rubber on the other side.

Zinc Oxide Plaster: This is similar to rubber adhesive plaster, but medicated with 20–30% of zinc oxide added to the adhesive compound.

Adhesive Plaster: This consists of medicated elastic cotton fabric, spread with an adhesive compound, which contains 20–30% of zinc oxide.

Plaster of Paris Bandage: This is also medicated cotton fabric plaster, rendered adherent to the skin by a suitable adhesive. This bandage is impregnated with at least 80% of exsiccated calcium sulfate. However, for general purposes all these surgical dressings are divided into six main categories according to their uses. These categories are further subdivided into sections, which include materials having a similar type of construction, as follows:

Absorbent bandages use layers of absorbent material on open or contaminated wounds to debride; they must be changed frequently. They may be classified as fabric absorbents, fibrous absorbents, combined fabric and fibrous absorbents, medicated absorbents, etc.

Gauge Bandage or Common Gauge Bandage (Circular, Spiral, etc.)

The most common type of bandage is the gauze bandage, a simple woven strip of material, or a woven strip of material with a Telfa absorbent barrier to prevent adhering to wounds. A gauze bandage can come in any number of widths and lengths and can be used for almost any bandage application, including holding a dressing in place. The United States Pharmacopeia lists it as a form in which Absorbent Gauze may be provided. It is prepared from type 1 Absorbent gauze in various widths and lengths.

Gauzes

Gauzes are usually absorbent dressings principally made from cotton fabrics. They can be either medicated or unmedicated. Medicated gauzes and also other medicated dressings are prepared by immersing the fabric in a solution of the medicament and drying off the solvent. Gauzes used for surgical dressings may be conveniently classified as follows (Fig. 8.9):

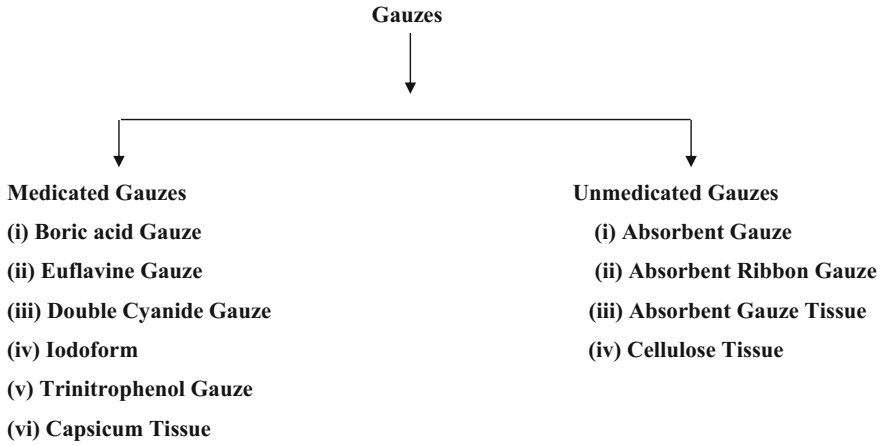

Fig. 8.9 Classification of gauges

Medicated Gauzes

Medicated gauzes are treated with the respective medicaments such as:

(i) **Boric Acid Gauze**: This gauze contains 3–7% of boric acid and tinted pink with a suitable dye.
(ii) **Euflavine Gauze**: This gauze is medicated with 0.1% of Euflavine.
(iii) **Double Cyanide Gauze**: This gauze contains a mixture of mercury cyanide (0.5–1.5%) and zinc cyanide (1.5–3.0%) and is tinted purple with a suitable dye.
(iv) **Iododorm Gauze**: This medicated gauze contains 4–6% of lodoform.
(v) **Trinitrophenol Gauze**: Trinitrophenol gauze is absorbent gauze impregnated with trini-trophenol and may be prepared by immersing absorbent gauze in a sufficient quantity of a solution of trinitrophenol 1.5–2.5% in distilled water to produce a gauze which is absorbent, uniformly medicated as far as possible, and contains from of trinitrophenol. The principal use of trinitrophenol is as an antiseptic for the skin before operations.
(vi) **Capsicum Tissue**: It contains 1.5–2.5% of *Capsicum* tissue: This is a tubular absorbent gauze, which encloses Capsicum cotton wool.

Unmedicated Gauzes

Absorbent Gauze: This gauze consists of cotton fabric of plain weave, bleached to white and purified, 36 inches wide, with not less than 19 threads per inch in the warp and 15 in the weft. One square yard of the gauze weighs not less than 11.6 g.

Absorbent Gauze Tissue: This is sleeve-like (tubular) absorbent gauze, which encloses a thick layer of absorbent cotton wool. The fabric used in this gauze has 12 threads per inch of weft. One pound of this gauze must have a superficial area of not less than 1800 sq. inch.

Cellulose Tissue: This is also tubular absorbent gauze like the gauze tissue. But it encloses a thick layer of cellulose wadding instead of absorbent cotton wool. Other specifications are similar to those of absorbent gauze tissue.

8.4.1 Compression Bandage

The term 'compression bandage' describes a wide variety of bandages with many different applications. Short stretch compression bandages are good for protecting wounds on hands, especially on fingers (Fig. 8.10).

Short stretch compression bandages are applied to a limb (usually for treatment of lymphedema or venous ulcers). This type of bandage is capable of shortening around the limb after application and is therefore not exerting ever-increasing pressure during inactivity. This dynamic is called resting pressure and is considered safe and comfortable for long-term treatment. Conversely, the stability of the bandage creates a very high resistance to stretch when pressure is applied through internal muscle contraction and joint movement. This force is called working pressure.

Long stretch compression bandages have long stretch properties, meaning their high compressive power can be easily adjusted. However, they also have a very high resting pressure and must be removed at night or if the patient is in a resting position.

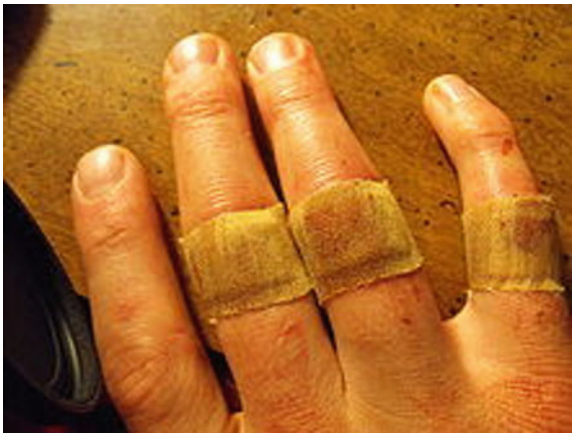

Fig. 8.10 Compression bandage on fingers

8.4.2 Triangular Bandage

Triangular bandage is also known as a cravat bandage, a triangular bandage is a piece of cloth put into a right-angled triangle, and often provided with safety pins to secure it in place. It can be used fully unrolled as a sling, folded as a normal bandage, or for specialized applications, as on the head. One advantage of this type of bandage is that it can be makeshift and made from a fabric scrap or a piece of clothing. The Boy Scouts popularized use of this bandage in many of their first aid lessons, as a part of the uniform is a 'neckerchief' that can easily be folded to form a cravat.

8.4.3 Figure-of-Eight Bandage

A bandage applied alternately to two parts, usually two segments of a limb above and below the joint, in such a way that the turns describe the Fig. 8.11, a specific bandage used for treatment of fractures of the clavicle (Fig. 8.11).

8.4.4 Tube Bandage

A tube bandage is applied using an applicator and is woven in a continuous circle. It is used to hold dressings or splints on to limbs or to provide support to sprains and strains, so that it stops bleeding.

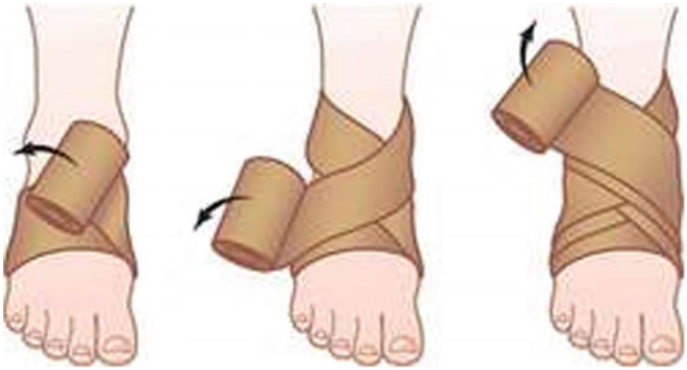

Fig. 8.11 Figure-of-eight bandage

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Chapter 9
Cultivation of Herbal Drugs, Biotechnology, and In Vitro Production of Secondary Metabolites, High-Value Medicinal Plants, Herbal Wealth, and Herbal Trade

Abstract Medicinal plants are used directly as therapeutic agents in various traditional practices, and medicinal plants like *Dioscorea deltoidea*, *Papaver somniferum*, *Atropa belladonna*, *Rauvolfia serpentina*, *Hyoscyamus niger*, *Digitalis lanata*, *Datura metel*, *Digitalis purpurea*, *Pilocarpusa bonandi*, *Cinchona ledgeriana* are contributing directly several prescribed medicinals. The ever-increasing trend in the use of medicinal herbs and herbal products in therapeutic purpose, research, and trade has created tremendous pressure on supply from their wild source. Under the circumstances of increasing demand, indiscriminate and over extraction from the wild, habitat destruction, etc., many of the naturally growing medicinal herbs are on the verge of extinction and thus unsustainability in the supply of medicinal plants from natural source. Systematic cultivation of medicinal herbs would be a viable alternative to overcome this unsustainability problem of medicinal plants from the wild source and cultivation offers opportunity to optimize yield and achieve a uniform, high-quality product. Several drugs like cardamom, cannabis, cinnamon, ginger, cinchona, opium, linseed, and fennel are now obtained almost exclusively from cultivation source. Benefits of cultivation of medicinal plants are widely viewed as a means for meeting current and future demands for large volume production of plant-based drugs; cultivation can reduce growing pressures on wild medicinal plants and ensure pure and smooth supply; means of earning livelihood, etc. The WHO has published wide-spectrum guidelines for good agricultural and collection practices for sustainable production of raw material of quality and standardized herbal ingredients to ensure quality of herbal medicines. Medicinal plants may be cultivated by the following: (a) agricultural practice at field level and (b) in vitro production of secondary metabolites. Commercial cultivation at field level (open field, homestead garden, forest floor) is an agronomic practice and offers the opportunity to overcome the problems that are inherent in herbal extracts like misidentification, genetic and phenotypic variability, extract variability and instability, toxic components, and contaminants. The agronomic method of crop cultivation includes systematically the steps like site and season selection, selection of crop, true seed or vegetative propagule, land preparation and basal manuring and fertilization, spacing, seed sowing or seedling transplantation,

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split application of fertilizer, irrigation, intercultural operation, and weed control and harvesting. Large-scale plant tissue or organ culture for the production of secondary metabolites is an attractive alternative approach to traditional methods of cultivation of drug plants. The advantages of this method are many; it is independent of soil, paste, climatic interference, geographical location, and it can ultimately provide a continuous and reliable source of natural products. Considering the cost involvement, plant tissue culture for secondary metabolites is now limited to only high-value compounds such as diosgenin-derived steroid hormone precursors, digitalis glycosides, berberine isoquinoline alkaloid, taxol, paclitaxel, and several other toxoids—complex diterpene alkaloids. Herbal plants have global market worth about US$62 billion per annum, and so they may be a good export item and wealth of a country and should be cultivated in commercial scale like any other conventional cash crops. As cultivation of medicinal plants at commercial scale is comparatively a new concept in many countries to meet the demand of internal and foreign markets and earning livelihood of the rural people, medicinal plants are important natural wealth and herbal wealth, play significant role in providing primary health-care services to rural people, and serve as raw material in traditional and modern pharmaceutical as well as in cosmetic, agricultural, and food industries. Substantial amount of foreign exchange can be earned by exporting medicinal plants to other countries. In this way, indigenous medicinal plants may play a significant role in the economy of a country.

Keywords Medicinal plant cultivation · Genetic erosion · Habitat destruction · GACPs

9.1 Field-Level Cultivation of Medicinal Plants

Cultivation of medicinal plant is gaining popularity because of the worldwide use of herbal medicine and high demand of herbs in the internal and world market. Musk mallow (*Abelmoschus moschatus*), senna (*Cassia senna*), ashwagandha (*Withania somnifera*), long pepper (*Piper longum*), black pepper (*Piper nigrurm*), Indian goose berry (*Emblica officinalis*), king of bitters (*Andrographis paniculata*), Indian borage (*Coleus amboinicus*), Rauvolfia (*Rauvolfia serpentina*), yam (*Dioscorea deltoidea*), opium poppy (*Papaver somniferum*), deadly nightshade (*Atropa belladonna*), heart-leaved moonseed (*Tinospora cordifolia*), Gymnema (*Gymnema sylvestre*), wood apple (*Aegle marmelos*), black oil plant (*Celastrus paniculatus*), Asparagus (*Asparagus racemosus*), Aloe (*Aloe vera*), drum stick (*Moringa oleifera*), basil (*Ocimum basilicum*), Indian pennywort (*Bacopa monnieri*), Calendula (*Caledula officinalis*), longevity spinach (*Gynura procumbens*), daruharidra (*Berberis aristata*), guggal (*Commiphora wightii*), jatamansi (*Nardostachys jatamansi*), jatropha (*Jatropha carcus*), saffron (*Crocus sativus*), lavender (*Lavedula*

angustifolia), lemongrass (*Cymbopogon citrtus*), parsely (*Petroselinum crispum*), Stevia (*Stevia rebaundiana*), Vanilla (*Vanilla planifolia*), licorice (*Glycerrhiza glabra*), neem (*Azadirachta indica*), foxglove (*Digitalis purpurea*), Eucalyptus (*Eucalyptus globules*), tobacco (*Nicotiana tabacum*), periwinkle (*Catharanthus roseus*), rose (*Rosa damascene*), coriander (*Coriandrum sativum*), *colocynth* (*Citrullus colocynthes*), fennel (*Foeniculum vulgare*), *senna* (*C. senna*), Calabar bean (*Physostigma venenosum*), nux vomica (*Strychnos nux-vomica*), castor bean (*Ricinus communis*), kurchi (*Holarrhena antidysenterica*), cinnamon (*Cinnamomum zeylanicum*), henbane (*Hyoscyamus niger*), bitter-wood (*Quassia amara*), sandalwood (*Santalum album*), ipecac (*Carapichea ipecacuanha*), turmeric (*Curcuma longa*), zinger (*Zingiber officinale*), valerian (*Valeriana officinalis*), mayapple (*Podophyllum peltatum*), *Artemisia annua*, *Taxus wallichiana*, *Strophanthus* spp., *Chondrodendron tomentosum*, *Cinchona* spp., etc., are some of the common herbs used in manufacture of herbal drugs and active constituents of modern drugs.

Many medicinal plants of therapeutic importance are low input economically important medicinal crops. They are presently cultivated commercially in different countries along with traditional agricultural and horticultural crops as sole crops, intercrops, sequential crops, mixed crops, etc., as well as in the agroforestry systems. Agroforestry systems have the advantage over agricultural systems because of the presence of a wide range of ecological niche or microclimates ranging from nearly full sun, partial shade, and partial sun to full shade (heliophyte–sciophyte). A specific crop can be located in near-ideal conditions as close to its natural habitat as possible. Many countries have developed a number of high-yielding varieties, worked out agrotechnologies and processing technologies for cultivation of HYV medicinal and aromatic plants.

Cultivation of medicinal plants requires intensive care and management. The conditions and duration of cultivation required vary depending on the quality of medicinal plant materials required. If no scientific published or documented cultivation data are available, traditional methods of cultivation should be followed, or a method should be developed through research. Factors that affect medicinal plant cultivation are altitude, temperature, rainfall, humidity, irrigation, soil types and fertility levels, fertilizers, pest and pest control, plant hormones, polyploidy, green house effects, hybridization, etc. Conservation Agriculture (CA) techniques (resource-efficient/resource-effective agriculture) including 'no-tillage' systems should be followed where appropriate, especially in the build-up of organic matter and conservation of soil humidity. CA aims to conserve, improve and make more efficient use of natural resources through integrated management of available soil, water and biological resources combined with external inputs. The principles of good plant husbandry including that of WHO on good agricultural and collection practices (GACPs) may be followed, and tillage should be adapted to plant growth and other requirements.

9.1.1 WHO's Guidelines on Good Agricultural and Collection Practices (GACPs)

The WHO has published guidelines for GACPs for medicinal plants, and member countries are required to develop country-specific guidelines for sustainable production of raw material of quality and standardized herbal ingredients to ensure quality of herbal medicines and ecologically sound cultivation practices. The GACPs cover a wide spectrum of cultivation and collection activities.

Some Basic Guidelines Under GACPs for Cultivation of Crop
Selection of proper site for cultivation of a particular medicinal plant, selection of correct time for cultivation, selection of proper variety, adoption of organic farming, etc., are considered important for cultivation.

GACPs for Collection (Harvest)
For collection, only desired mature part(s) to be selected without harming the mother plant and whole population (at least 30–40% to be left for regeneration), twigs/branches are not to be cut for the collection of plant parts, proper equipment is necessary for cutting, shearing, peeling, etc. Collected material should be cleaned (removal of dust and other undesirable matter), sun dried, or processed immediately after collection up to complete drying before packing and storage, but aromatic herbs and delicate fruits in shade separately (two or more herbs not in close vicinity). Herbs should be packed in suitable packaging material to avoid losses due to external factors and to be stored in proper storage conditions to minimize loss on storage.

Collection of Underground Part(s), Bark, and Whole Plant
To facilitate regeneration, collection should be made after seed shed, collection of the underground part should be done when the mother plant fully matures, digging should be minimum and to facilitate regeneration, some parts to be left underground, fleshy parts should be dried before packing and storing, large parts should be cut into smaller pieces, bark should be collected not from immature plant, instead, from the branches of main trunk, strip the bark longitudinally and not from all over the circumference of trunk/branches, to be cut into small pieces to facilitate complete drying, only mature branches for stem is recommended for harvest, and herbs are to be dried properly before packing or storing.

Collection of Leaves, Flowers, Fruits, Seeds, Floral Parts, etc
For collection of leaves, flowers, fruits, seeds, floral parts, etc., only mature parts from healthy plants are to be selected for harvest and not collect all material of the plant at a time, and it is advised not to cut branches for collecting leaves, fruits, flowers, and so on; some floral parts on the plants are to be left to facilitate natural regeneration, fleshy flowers may be dried in the sun, but shade is preferable. Parts like stigma, anthers, buds, etc., should be collected at appropriate time and seeds, when the fruits are completely mature.

Collection of Gums, Oils, Resins, Galls, etc

For collection of gums, oils, resins, galls, etc., incisions should be made only vertically on some portions of the tree and not horizontally; the incisions to be treated after collection of the desired material; the gum or resin not to be collected from a tree continuously but precisely in right season; gum or resin not to be left exposed in the field; but to be packed in appropriate containers or drums with polyethylene lining; the galls are to be collected only from prescribed species (e.g., Karkatshringi from *Pistacia integerrima*), and no live insect should be present inside the galls.

9.1.2 Necessity, Benefits, and Limitations of Commercial Cultivation of Medicinal Plants

Medicinal plants are the oldest known health-care products, and their importance is still growing all over the world. Medicinal plants have been playing a significant role in Ayurveda and Unani systems of medicine in Indian subcontinent, Chinese traditional medicine, Kampo of Japan, and other traditional systems of medicine developed by the indigenous people of many countries of Europe, America, Australia, and Africa since long past. The World Health Organization (WHO) supports Member States in their efforts to formulate national policies on traditional medicine taking into accounts its potential, safety, efficacy, etc. A genuine interest in various traditional practices now exists among practitioners of modern medicine. A survey among Member States of the European Union in 1991 identified about 1400 herbal drugs used in the European Economic Community. Medicinal plants are important for pharmacological research and drug development directly as therapeutic agents as well as basic materials and models for the synthesis of drugs and pharmacologically active compounds, respectively. Some of the important medicinals from plant sources are enlisted in Table 9.1.

Consumption of herbal medicines is widespread and increasing. Naturally growing medicinal plants are collected for use in traditional medicine and in pharmaceutical industries. Indiscriminate and over extraction from the wild by uneducated and unskilled local people is a major cause of loss of genetic diversity (genetic erosion) and habitat destruction and thus unsustainability, and it is also downgrading the herbal products due to adulteration, inferiority, substitution, admixture, etc. Local communities, traditional medicinal herbalists, and herbal medicine vendors popularly collect roots, bark, and whole shrubs, and thus subject the naturally grown plant species in the verge of extinction. The uncontrolled collection and sale of large quantities of plant material from the forest leads to the destruction of many forest plants. These problems associated with wild medicinal plants have necessitated systematic cultivation of many medicinal plants, and domestic cultivation is a viable alternative to overcome the problems that are inherent in the production of herbal medicines including species misidentification,

Table 9.1 Some most common medicinals from plant sources

Medicinal plant source	Medicinals	Activity
Aglaia foveolata	Silvestrol	Cytotoxic
Artemisia annua	Artemisinin	Antimalarial drug
Atropa belladonna	Atropine	Anticholinergic
Camptotheca acuminata	Camptothecin	Antitumour
Capsicum frutescens	Capsaicin	Counterirritant
Cassia angustifolia	Sennosides A and B	Laxative
Cassia quinquangulata	Resveratrol	COX-1 enzyme inhibitor
Castanospermum australe	Castanospermine	Glycoside inhibitor
Catharanthus roseus	Ajmalicine	Antihypertensive
Catharanthus roseus	Vinblastine, vincristine	Anticancer
Cephaclis ipecaccuanha	Emetine	Powerful emetic
Cinchona spp.	Quinine, Quinidine	Antimalarial
Colchium autumnale	Colchicine	Antitumour
Coleus forskolii	Forskolin	Bronchial asthma
Coptis japonica	Berberine	Antibacterial, anti-inflammatory
Datura metel, *D. stramonium*	Scopolamine	Anticholinergic, antihypertensive
Digitalis lanata, *D. purpurea*	Digoxin, Digitoxin	Cardiotonic glycosides
Dioscorea deltoidea	Steroids	Antifertility agents
Erythroxylum pervillei	Pervilleine A	Anticancer
Galanthus woronowii	Galantamine	Anti-Alzheimer's drug
Hyoscyamus niger	Hyoscyamine	Anticholinergic
Lithospermum erythrorhizon	Shikonin	Antibacterial, Antiseptic
Orchrosia elliptica	Ellipticine	Antitumor
Panax ginseng	Ginsenosides	Health tonic
Papaver somniferum	Opium alkaloids, Codein	Analgesic, antitussive, sedative
Pilocarpus abonandi	Pilocarpine	Cholinergic
Podophyllum petalum	Podophyllotoxin	Antitumor
Rauvolfia serpentina	Reserpine	Antihypertensive
Sanguinaria canadensis	Sanguinarine	Antiplaque
Taxus brevifolia	Taxol	Anticancer drug
Trichosanthes sp.	Trichosanthin	Cytotoxicity against HIV-infected cells

genetic and phenotypic variability, variability and instability of extracts, toxic components, and contaminants. Cultivation offers the opportunity to optimize yield and achieve a uniform, high-quality product. Several plant-derived drugs like cardamom, cannabis, cinnamon, ginger, cinchona, opium, linseed, and fennel are now obtained almost exclusively from cultivated plants. Medicinal plants play a central

role as therapeutic agents and also as trade commodities of the international markets. Cultivation of medicinal plant is gaining ground because of the sky rocketing prices of allopathic medicines which also have side effects. Cultivation of medicinal plants is widely viewed as a means for meeting current and future demands for large volume production of plant-based drugs and herbal remedies, and also as a means for relieving harvest pressure on wild populations (Palevitch 1991; WHO/IUCN/WWF 1993; FAO 1995; Lambert et al. 1997; de Silva 1997).

Benefits of Commercial Cultivation of Medicinal Plants

Cultivation Can Reduce Growing Pressures on Wild Medicinal Plants

The World Health Organization (WHO) has estimated that more than 80% of the world's population in developing countries depends primarily on herbal medicine for basic health-care needs, and the use of herbal medicines in developed countries is also growing; about 25% of the UK population takes herbal medicines regularly (Vines 2004). Approximately two-thirds of the 50,000 different medicinal plant species in use are collected from the wild (Edwards 2004) and, in Europe, only 10% of medicinal species used commercially are cultivated (Vines 2004). There is growing concern about diminishing populations, loss of genetic diversity, local extinctions, and habitat degradation. Well-known species threatened by wild harvesting include *Arcostaphylos uva-ursa*, *Piper methysticum*, and *Glycyrrhiza glabra* (Vines 2004). Between 4000 and 10,000 medicinal species might now be endangered (Edwards 2004).

Ensures Pure and Smooth Supply

Importance of cultivation of medicinal plants may be justified on the basis of the following points. (i) It ensures a correct natural source of the drug. (ii) The process of collection and harvesting of the drugs can be effectively monitored under cultivation, i.e., they can be collected at the right time and in the proper manner. (iii) Drying and storage of the drugs from cultivated sources can be more effectively regulated and controlled ensuring the production of good-quality drugs. (iv) Purity of the finished product is assured under cultivation as weeds and other contaminants can be removed by careful weeding during the growth of the crop. (v) Quality and production of the drug can be improved under cultivation by the selection of high-yielding and disease resistant seeds and varieties, by the use of natural and synthetic fertilizers, which increase the total yield of the plants and their active constituents, e.g., nitrogenous fertilizers increase alkaloid content of Solanaceous plants and by the production of hybrids with high-yielding and disease resistant properties. (vi) Cultivation ensures constant and regular supply of genuine drugs. (vii) Prices of crude drugs and monopolies of their production can be controlled and reduced by cultivation. (viii) Illegal trade of dangerous drug like cannabis and opium can be restricted by controlled cultivation of such drugs. As evident from these points, it is preferable that crude drugs are obtained from cultivated sources.

Means of Earning Livelihood

Cultivation of medicinal plants is economically very attractive. Advantages of commercial of medicinal plants over wild harvest for production of plant-based medicines include (i) wild collection often offers material adulterated with unwanted, sometimes harmful other plant species while cultivation provides reliable botanical identification and production of uniform materials; (ii) wild harvest volumes are dependent on many factors that cannot be controlled and the irregularity of supply is a common feature while cultivation guarantees continuity and steady supply of raw material; (iii) wholesalers and pharmaceutical companies can agree on volumes and prices over time with the grower; (iv) the selection and development of genotypes with commercially desirable traits from the wild or managed populations may offer opportunities for the economic development of the medicinal plant species as a crop; (v) cultivation allows controlled post-harvest handling and therefore (vi) quality controls can be assured through cultivation; (vii) cultivation can provide opportunities for value addition through processing; (viii) product standards can be adjusted to regulations and consumer preferences; (ix) cultivated material can be easily certified organic or biodynamic, although certifiers are also presently developing wild crafting standards; (x) commercial cultivation of medicinal plants helps to conserve endangered species in their natural habitat; (xi) provides good income to the farmers; and (xii) provides a better environment through utilizing waste and unproductive lands (Palevitch 1991; Pierce et al. 2002).

Limitations of Commercial Cultivation

The principal disadvantages of cultivation of medicinal include (i) failure of crops due to (i) adverse weather conditions such as flood, drought, frost, or heavy rain during growth and harvesting seasons; (ii) fungal and viral diseases which spread rapidly among closely growing plants of the same species, e.g., attack of Belladonna by *Phytophthora* species; (iii) large-scale damage of the crops by the attack of insects (like the flea beetle) and rodents in the field; (iv) high production cost; and (v) lack of required environmental conditions for cultivation of a particular medicinal plant. For example, Indian hemp requires a typical tropical climate for the production of the narcotic resin. However, all these drawbacks, which are also common to other cultivated crops, should not discourage the cultivation of drug plants as the benefits derived from cultivation greatly outweigh these disadvantages. Beside these limitations, there are some other constraints to commercial cultivation of medicinal plants.

As compared to other economic crops, medicinal plants have received much less attention in genetic and cultural improvements. Only a few countries are now cultivating improved cultivars, while the rest still depend on wild material collected for cultivation. Their cultivation techniques are quite primitive, resulting in poor yield and quality of the materials. Several constraints include (i) biotic—unimproved cultivars, long life cycle, susceptibility to pests and diseases; (ii) abiotic—low soil fertility, flood and drought, improper light intensity and duration, extremes of temperatures, and physical injuries or damage; (iii) technological—lack of good agronomic practices, lack of technology and technology transfer, and lack of

facilities; and (iv) socioeconomic—competition with other economic crops and modern drugs; lack of market channels, a domestic pharmaceutical industry, and organized cultivation and no price support. In spite of these constraints, medicinal plants continue to play a significant role in the welfare of rural people in Asia and other parts of the world. Due to higher demand of raw material for industrial processing coupled with the loss of natural habitats of most medicinal plants, large-scale cultivation of promising species has recently been attempted in several countries.

9.1.3 Factors Affecting of Cultivation of Medicinal Plants

Cultivation of some herbs has proved difficult because of low germination rates or specific ecological requirements (Vines 2004). There could simply be a lack of knowledge about the specific requirements for pollination, seed germination, and growth. Low germination rates frequently result from fungal infection or mechanical damage to seeds and can be improved by seed treatments and by ensuring optimum storage conditions. Stratification, the artificial emulation of environmental conditions required for seed germination such as soaking or chilling, can sometimes provide the key to success. In *Panax quinquefolium* (American ginseng), the use of a controlled environment substantially shortens the stratification period required, increases germination rate and seed viability, and enables seed germination at any time of the year (Li et al. 2000). Similarly, it might be necessary to optimize the conditions for pollinators or to conduct artificial pollination. The use of controlled environments including hydroponics could be one way in which difficult-to-grow medicinal plants can be cultivated on a commercial scale.

Other problems associated with cultivation of medicinal plants are in no way different from those associated with other agricultural crops. The factors that create great problems for cultivation of medicinal plants may be roughly divided into two groups: (a) climatic factors and (b) ecological factors.

Climatic Factors

The climatic factors that directly affect the growth of a plant include (i) altitude, (ii) temperature, (iii) sunlight, and (iv) rainfall.

(i) Altitude refers to the specific elevation of a land surface in comparison with the sea level. This factor influences the growth of plants very seriously, and thus, plants of different altitudes vary greatly from each other in type, nature, and constituents. A plant of the higher altitude cannot therefore be profitably cultivated in a land of lower altitude. (ii) Temperature influences plant growth considerably. Plants growing in a tropical climate do not normally survive in a temperate region. (iii) Sunlight or length of day or photoperiod plays a significant role in plants' growth and production of chemical constituents. Short-photoperiodic plants do not grow well under longer photoperiodic condition. (iv) Rainfall determines the type of vegetation of a region. Every plant requires enough rainfall for its growth and

survival, but the requirement varies from plant to plant. While rainfall is an important factor for plant growth, heavy rainfall or drought is highly detrimental to their growth, particularly under cultivation.

Ecological Factors

Ecological factors like soil condition, soil pH, and associated plant growth (weed) are of great importance in the cultivation of medicinal plants. Soils differ from each other both in physical and chemical properties and may be a clay or loamy soil. The loamy soils may be either sandy barns or loamy sands. These different soils have different water retention capacity which determines the type of plants grown or cultivated in them. Selection of the correct type of soil, which is not always practicable, is very important in the cultivation of various plants including the medicinal ones. Weeds often pose a serious problem in the cultivation of medicinal plants. They affect the crop adversely in a number of ways: (i) use up the essential food elements and manures used for cultivation and thus compete with the drug plant; (ii) prevent sunlight reaching the drug plant; (iii) choke the drug plant by occupying essential land space; (iv) introduce difficulty in collection and contaminate the collected drug, and (v) attract and harbor insects, fungus, and other microorganisms.

Cultivation of medicinal plants especially high-value medicinal plants is creating new dimension in the field of agriculture. For active drug principles of therapeutic importance, medicinal plants are now cultivated following: (a) field-level cultivation through agricultural practices and (b) biotechnology and in vitro production of secondary metabolites.

9.1.4 Field-Level Commercial Cultivation of Medicinal Plants (e.g., Rauvolfia Serpentine*,* Cinna *spp.,* Atrpa Belladonna, and Catharanthus Roseus*)*

Commercial cultivation at field level (open field, homestead garden, forest floor) is a viable alternative and offers the opportunity to overcome the problems that are inherent in herbal extracts like misidentification, genetic and phenotypic variability, extract variability and instability, toxic components, and contaminants. Field crop cultivation in a scientific way at field level is an agronomic practice. Agronomy is the science and technology of crop producing in the field for food, fuel, fiber, and others. Agronomy encompasses work in the areas of plant genetics, plant physiology, meteorology, and soil science. The agronomic method of crop cultivation includes systematically the following steps: selection of seeds or propagules of the desired crop, land preparation and basal manuring and fertilization, spacing, seed sowing or seedling transplantation, split application of fertilizer, irrigation, intercultural operation, and weed control and harvesting.

Cultivation of medicinal plants involves all the common processes and methods utilized for cultivation of other agricultural crops. They can be cultured by true seeds as well as by vegetative propagules.

Some of the Basic Steps of GACPs for Medicinal Plants

(i) Selection of medicinal plant for cultivation,
(ii) Botanical identity,
(iii) Seeds and other propagation material,
(iv) Method of cultivation,
(v) Harvest, and
(vi) Personnel.

(i) Selection of medicinal plant for cultivation

Species or botanical variety selected for cultivation should be same as that specified in national pharmacopoeia or recommended by other authoritative national documents of the end—user's country. In case of newly introduced medicinal plant, the species or botanical variety selected for cultivation should be identified and documented as the source material used or described in traditional medicine or the original country.

(ii) Botanical identity

Scientific name (genus, species, subspecies/variety, cultivar, family) should be verified and recorded. Cultivar name, ecotype, chemo-type, or phenotype may also be provided, as appropriate name of the material supplier should be recorded. In case of land races collected, propagated, disseminated, and grown in a specific region, records are kept of the locally named lines, including the origin of the source seeds plants or propagation material.

(iii) Seeds and other propagation material

All information relating to identity, quality, and performance (as well as breeding history where possible) of the propagation material (seed or vegetative propagule) is obtained from the supplier and recorded. Planting material should be free from contamination and disease to promote healthy plant growth. It is necessary to be careful to exclude extraneous species, variety, or strain. Any genetically modified germplasm should comply with regional and/or national regulations and be appropriately labeled and documented, as required.

(iv) Method of cultivation

If no scientific published or documented agrotechnology data are available, traditional method of cultivation to be followed or agrotechnology is developed through research work. Principles of good plant husbandry, including appropriate rotation of plants selected according to environment suitability, should be followed. Conservation agriculture technique (CA) is followed where appropriate, particularly in the build-up of organic matter and conservation of soil humidity. CA aims to

conserve, improves, and makes more efficient use of natural resources through integrated management of available soil, water, and biological resources combined with external inputs. It contributes to environmental conservation as well as to enhanced and sustained agricultural production. Cultivation process involves site selection, ecological and social impact, climate, soil, irrigation and drainage, plant maintenance, and protection.

Site Selection

When cultivated at different sites, same medicinal plant may exhibit differences in quality due to soil, climate, and other factors. These differences may relate to physical appearance or to variations in their constituents. Risk of contamination as a result of pollution of soil, air, or water by hazardous chemicals should be avoided. The impact of past land uses on cultivation site, including the planting of previous crops and any application of plant protection products, should be evaluated.

Ecological and Social Impact

The ecological impact of cultivation should be monitored overtime, where practical because cultivation of medicinal plants may affect ecological balance and in particular, the genetic diversity of the flora and fauna in surrounding habitats; the quality and growth of medicinal plants can also be affected by other plants, living organisms, or by human activities, etc. Introduction of non-indigenous medicinal plant species into cultivation may have a detrimental impact or biological and ecological balance of the region. The social impact of cultivation on local communities should be examined to ensure that negative impacts on local livelihood are avoided. In terms of local income—earning opportunities, small-scale cultivation is preferable to large-scale cultivation provided the small-scale farmers are organized to market their products jointly. In case of the establishment of large-scale cultivation of medicinal plants, care should be taken for local communities benefit for fair wages, equal employment opportunity, and others.

Climate Conditions

Climate conditions, e.g., length of the day, rainfall (water supply), and field temperature, significantly influence the physical, chemical, and biological qualities of medicinal plants; duration of sunlight; average rainfall; average temperature; and anytime and night time temperature differences influence the physiological and biochemical activities of plants and prior knowledge should be considered.

Soil

Soil should contain appropriate amounts of nutrients, organic matter, and other elements to ensure optimal medicinal plant growth and quality; optimal soil conditions including soil type, drainage, moisture retention, fertility, and pH should prevail; correct type and quantity of fertilizers are necessary with minimum risk of leaching; human excreta as fertilizer to be avoided due to potential presence of infectious microorganisms and parasites; and animal manure should be thoroughly composted to meet safe sanitary standards of acceptable microbial limits

Irrigation and Drainage
Irrigation and drainage should be controlled and carried out in accordance with the needs of the individual medicinal plant species during its various stages of growth. Water used for irrigation should comply with local, regional, and or national quality standards. For choice of irrigation, as a general rule, the health impact of different types of irrigation (various forms of surface, subsurface or overhead irrigation), particularly on the risk of increased vector-borne disease transmission, must be taken into account.

Plant Maintenance and Protection at Field Level
Plant maintenance and protection at field level (e.g., timely topping, bud nipping, pruning, and shading) should be in favor of the growth and development characteristics of medicinal plant as well as part of the plant destined for medicinal use to improve the quality and quantity of medicinal plant material. Use of any agrochemical for growth promotion and protection should be kept to the minimum. Integrated pest management should be followed. When necessary, only approved herbicide/pesticide is applied at minimum effective level as per label instructions. All applications should be documented. Growers should comply with maximum pesticide/herbicide residues

(v) Harvest

Time of harvest depends upon the plant part to be used and for that national pharmacopoeia, official monographs, and published standards may be consulted. MPs parts are to be harvested during optimum season or time period to ensure best quality of harvested material. Concentration of bioactives varies with the stage of plant growth and development. Best time for harvest (quality peak season/time of day) should be based on maximum concentration of bioactive principles. During harvest, no foreign matter, weeds, or toxic plants are not to be mixed with the harvest and dew, rain, humidity, etc., should be avoided during harvest. Immediate drying after harvest is advisable. Cutting devices, harvesters, and other mechanical devices should be clean and adjusted to reduce damage and contamination from soil and other material. Storage under uncontaminated dry place free from insects, rodents, birds, and other pests and inaccessible to livestock and domestic animals is recommended. Contact with soil and humidity to be avoided to minimize microbial load in harvested material. Clean baskets, dry sacks, trailers, hoppers, or other well-aerated containers are suggested for use for transporting harvested material to central place. Any decomposed material should be discarded.

(vi) Personnel

Growers and producers should have adequate knowledge of the MAPs including botanical identification, cultivation characteristics, and environmental requirements. Growers and producers should receive and abide by the instructions on all issues relevant to the protection of the environment, conservation, and proper agricultural stewardship for producing quality MAPs material. All personnel (including field workers) involved in propagation, cultivation, harvest, and post-harvest stages

should maintain appropriate personal hygiene and should have received training regarding their hygiene responsibilities and in MAPs cultivation and harvesting.

Cultivation by True Seeds
Like any other crops, drug plants are raised from seeds. This method of propagation involves different steps, e.g., selection of seeds, preparation of seed beds, sowing of seeds, and transplantation of the seedlings, irrigation and weeding, protection of the crop and harvesting.

Cultivation by Vegetative Propagules
Cultivation by vegetative propagules or organs involves a number of methods including cuttings, layers, grafting and budding, fermentation.

Vegetative Organs
Cultivation of medicinal plants may be done by various vegetative organs like bulbs, corms, tubers, rhizomes. Vegetative organs are planted in large numbers to raise a crop such as (i) by division or separation of a plant into its individual constituent aerial stems or buds (each having roots and a growing point) and planting them separately, (ii) by bulbs as is done in the propagation of garlic, onion (*Alium sativum*, *A. cepa*), rhubarb (*Rheum rhabarbarum*), squill (*Drimia maritime*), and gentian (*Gentiana* spp.); (iii) by runners or offsets as produced by many plants like cocoyam (*Colocasia esculenta*, *Xanthosoma* spp.), mints (*Mentha longifolia*), etc., when the runners with the daughter plants are detached from the mother plant and planted, (iv) by suckers or stolons—in this case, the suckers are separated from the mother plant and planted separately as in liquorice (*G. glabra*), (v) by corms as in coichicum, teliga potato (*Colchicum speciosum* and other species, *Amorphophallus bulbifer*), (vi) by tubers as in winter aconite (*Eranthis* spp.), and (vii) by rhizome as in ginger (*Z. officinale*).

Cuttings
Cuttings are made by severing a stem (or root) into many parts, each having at least one node. On dipping into soil, roots and buds develop from the nodes. This method is applied in propagating large number of plants, e.g., rose, grapes, coca, and snakeroot.

Layers
In this method, a branch or shoot is induced to produce roots by partly interrupting the food supply by removing a portion of the bark at one part of the stem. This part is then embedded or covered with soil and regularly supplied with water. When roots develop at the treated part, the stem is severed from the plant with the roots and then planted. Propagating plants by means of layers always ensures exact duplication of the mother plant. This is a popular method of propagation, particularly with fruit trees.

Grafting and Budding
These are not commonly used for propagation of medicinal plants, except for some experimental purposes. Grafting is a method of growing the foliar parts of one plant, termed as action, on the main or side stem of another related plant, called the

stock. In making a graft, two stems of equal size and age of two related plants are cut obliquely using a sharp knife or a razor blade to ensure a clean cut across. The severed parts are then exchanged, fitted together, tied with a string, and covered. In a few weeks time, the scion and the stock arc naturally joined and the wound health. In budding, a piece of bark bearing a bud is removed from one plant and is introduced into a suitable cavity or a 1-shaped slit made in the bark of another plant or stock, which finally bears the developed bud. This is largely used in citrus plants for growing sweet orange branches on sour stocks.

Fermentation

Mold and bacteria are propagated by a process called fermentation. In this method, strains of the microorganisms are allowed to grow by seeding a small amount of the selected strain in a suitably prepared liquid nutrient medium.

Farming for Cultivation of Medicinal Plants

World needs eco-friendly farming systems for sustainable agriculture, sustainable from environmental, production, and socioeconomic points of view. Sustainable agriculture has become the umbrella under which many alternative farming systems (e.g., organic, biological, regenerative, alternate, ecological, low input agriculture) fall. Sustainable agriculture system reduces environmental degradation, maintains agricultural productivity, promotes economic viability in both the short and long term, and maintains stable rural communities and quality of life as well as emphasizes the conservation of its own resources. Sustainable farms minimize their purchased inputs (fertilizers, energy, and equipment) and rely, as much as possible on the renewable resources of the farm itself without any adverse effect on bio-physical resources including soil, water, and biota of the environment. It embraces several forms of non-conventional agriculture that are often called organic, alternative, ecological, or low input.

Medicinal Plants the First Crops for Organic Farming

Organic farming in dry lands can be started with medicinal plants because

(i) The forest resource of medicinal plants is decreasing, but demand is increasing thus cultivation is the only solution to fill this gap;
(ii) Medicinal plants are for the curing of disease and any residue of pesticide can convert it into poison. Hence, medicinal plants should only be cultivated in organic farming; and
(iii) Use of high dose of inputs like fertilizers, irrigation may change the composition and quality of medicinal plants. Growing near to natural conditions is the best way to maintain the quality, which is possible in the organic farming.

(i) Cultivation of *Rauvolfia serpentina*

Sarpagandha or snakeroot (*R. serpentina* Benth. Ex Kurz, $2n = 22$, of Apocynaceae) is an important medicinal plant distributed in the moist deciduous forests of Southeast Asia including Bangladesh, India, Myanmar, Sri Lanka, Thailand, Malaysia, the Andaman Islands, and Indonesia. In Bangladesh, it is found

in the foothills of greater Chittagong and Sylhet districts, in Sal forest and in many parts of the country. It is an erect evergreen, perennial under-shrub, 75 cm to 1 m in height. The root system of *R. serpentina* consists of a prominent, tuberous, soft taproot, reaching a length of 40–60 cm deep into soil in a 2 year old plant. Its diameter at the thickest portion varies from 1.2 to 2.5 cm. The root, especially the root bark, possesses high alkaloid concentration (40–60% of the whole root). Root contents of alkaloids vary from 1.7 to 3% of the dry roots. The fresh roots emit a characteristic acrid aroma and are very bitter in taste. The world requirement of dried *Rauvolfia* roots is about 20,000 t/year, but only about 400–500 tons of roots are presently collected annually from wild source (Poonam and Mishra 2013; Paturkar and Khobragade 2016).

In addition to *R. serpentina,* there are two other species, e.g., *R. tetraphylla* and *R. vomitaria*. Root of *R. serpentina* has a 400-year history of use in the treatment of snakebite, insect stings, nervous disorder, and others, and the alkaloids obtained from it have been recognized by the allopathic system in the treatment of hypertension and as a sedative or tranquillizing agent.

Climate

R. serpentina can be grown under a wide range of climate conditions. It flourished in tropical or subtropical hot, humid conditions and can be grown both in the sun and in partial shade. In its natural habitat, the plant thrives under the shade of forest trees. The best areas are those which combine high rainfall (250–500 cm) with properly drained soil. In low rainfall areas, the plant can be successfully cultivated with irrigation during the drier months. The plant is sensitive to water-logging, but it can withstand water for 2–3 days without too much damage. The plant sheds its leaves during the cold months in localities with severe winters. Frost kills the top tender, green twigs only, and fresh shoots sprout up with the advent of spring from the thicker shoots which can withstand the frost.

Soil

The plant grows in a wide variety of soils, from sandy alluvial loam, clay or clayey loam to red lateritic loam of stiff dark loam, but prefers soil rich in nitrogenous organic matter with good drainage. The plant produces thicker roots in black, stiff loam soils than in heavy clayey or sandy soil. Soils containing large quantities of sand retard the growth of the plants and make them more susceptible to root and leaf diseases. The ideal soil pH for this crop is acidic (pH 4.6–6.2), and alkaline soils (pH 8 or above) are not suitable for commercial cultivation.

Land Preparation

The plant requires slightly acidic to neutral soils for good growth with medium to deep well-drained fertile soils. Clay-loam to silt-loam soils, rich in organic content are suitable for its commercial cultivation. It grows well in frost-free tropical to subtropical situations under irrigation.

Propagation

The crop may be propagated by seed, stem cuttings, root stumps, and root cuttings. Seed propagation is the best method for raising commercial plantation.

Propagation by Seed

The *Rauvolifia* is usually propagated by seeds but irregular and low percentage of germination of seeds is the main difficulty in the propagation of. This is partly attributed to the adverse influence of the stony endocarp, absence of embryos due to parthenocarpy or somato-plastic-sterility.

Collection of Seeds

Rauvolfia fruits mature between July and November, and collection of mature seeds is usually done from September to February. Only a few fruits ripen at a time and, if they are not collected immediately, they are shed and lost. Therefore, the collection of ripe fruits is easy in plantation but laborious and costly from plants growing in the wild. After collection, the fruits are freed from their pulpy covering by rubbing them against old gunny bags or on rough flooring. The cleaned seeds are thoroughly dried in the sun and stored in dry places or in airtight containers; seeds thus stored in airtight bins, retained their viability for about 6 months. The viability of the seeds drops markedly with the increase in the interval of time between collection and sowing.

Seed germination in *Rauvolfia* varies from 10 to 60% even when only heavy seeds are chosen for sowing purpose. Light and heavy seeds can easily be separated by simple water flotation. Germination of heavy seeds during May–June after soaking them in water for 24 h was 20–40, and 74% germination was recorded in case of freshly collected fully matured heavy seeds. The germination rate of the seed also differs under varying agroclimatic conditions. Direct sowing of the seeds in the field has not been successful due to this variability of seed germination, and it is therefore suggested to develop seedlings in the nursery bed. In all, 6 kg of seeds are sufficient to raise one-hectare plantation.

Preparation of seed bed in nursery

The nursery should ideally be located in partially shaded areas with irrigation facilities. The land is cleared of weeds and plowed to a depth of 30 cm. Raised beds, each of 10 × 10 m dimension, are made containing one-third quantity of well-matured farmyard manures (FYM) and leaf mold, and two-thirds of medium-fine silt-loam soil. Seeds should be soaked in water overnight before sowing and light seeds which float can be discarded. The seeds can be treated with Thiram, a non-systemic fungicide, at the rate of 3 g/kg of seeds. About 5.5 kg of seeds sown in a 500 m^2 area will yield seedlings sufficient to plant one hectare. The seeds are sown 2–3 cm apart in rows in shallow furrows in the middle of May. The furrows are then covered with a fine mixture of soil and FYM, and the bed was kept just moist by light irrigation. The germination is gradual, starts after 15–20 days and continues up to 40–45 days, and the growth of the seedlings is slow. Seedlings are ready by mid-July for transplanting.

Propagation by vegetative propagules

Propagation by vegetative propagules like root or shoot cuttings has been advocated for easy propagation and quick multiplication of the genetically superior clones. Alamgir and Ahmed (2005) described the easy way of propagule development from

R. serpentina by stem (42.85%), root (62.82%) and stem-root junction (78.57%) cuttings. Pretreatment of cuttings by rooting hormones like NAA (10 ppm), IBA (50 ppm) or 2, 4-D (5 ppm) may increase the number of % of successful propagules.

Propagules Development in the Nursery Bed

Large taproots with a few filiform lateral secondary rootlets or stem are used. Nearly 2.5–5.0 cm long (or more up to 15 cm long and 2.5 cm diameter from 1.5- to 2-year-old plant) root or stem cuttings are planted during spring season in nursery beds containing well matured FYM, sand, and saw-dust. The beds are kept moist through watering. The cuttings begin to sprout within 3 weeks. These can be planted in field during rainy season after 8–10 cm rains are received; the seedlings are transplanted at 45-cm row-to-row and 30-cm plant-to-plant distance. In this manner, an estimated 100 kg of root or stem cuttings is found sufficient for planting one-hectare area. Direct plantation of cuttings may be done but seedlings developed from root or stem cuttings in nursery is more preferable for uniform population.

Transplantation

Seedlings of 40–50 days, which have 4–6 leaves, are ready for transplanting by mid-July. The seedlings are carefully dug out, and the top root should be cut. They are then dipped in a 0.1% fungicide solution to avoid soil-borne fungus causing damping-off disease. Well-rotten FYM at 25–30 t/ha is added during land preparation. The field is then divided into small plots for irrigation. About 15-cm-deep furrows are dug at a distance of 45 cm. The seedlings are transplanted in rows into the furrows in holes large enough to receive the seedlings along with the accompanying clump of earth at 30 cm distance (45 × 35 cm = space between rows and plants). The seedlings are buried up to the first pair of leaves, and soil around them is lightly pressed. Irrigation after transplanting is essential for better stand. *Rauvolfia* is long-duration (18 months) and slow-growing crop particularly in the initial stage; thus, different intercrops have been tried.

Manures and Fertilizers

The medicinal plants have to be grown without chemical fertilizers. The use of organic manure (decomposed leaf and compost, FYM, green manure, vermi-compost, etc.) has been recommended to increase the quantity of nutrients in the soil and improve the drainage. Initially before sowing, 10–15 tonnes of FYM/ha are used. However, the plant responded better to chemical fertilizers than to organic manures. Nitrogenous fertilizers induce more vegetative growth, followed by organic manure. Nitrogen fertilizer in combination with FYM and phosphates results in better root growth than nitrogen alone. Application of phosphates induces more growth of thick as well as thin roots. It is suggested to apply 25–30 t of FYM at the time of land preparation and 10 kg N, 60 kg P_2O_5, and 30 kg K_2O/ ha as a basal dose. Later two equal doses of N, each of 10 kg/ha in moist soil is given at 50 and 170 days after planting.

Irrigation

Rauvolfia can be raised as rainfed crop under subtropical conditions if the growing area receives 150 cm or above rainfall distributed uniformly throughout the growing season. It needs regular irrigation that is necessary under tropical condition with high temperature and low rainfall. About 15–16 irrigations at 20-day interval in summer and at 30-day interval in winter are suggested. The crop can be cultivated under rainfed conditions also, but the yield is considerably poorer.

Intercropping

It is possible to grow intercrops in *Rauvolfia* plantation, particularly where good irrigation facilities are available. It is reported that although the yield of roots was higher under monoculture, but the highest net return is possible when *Rauvolfia* was intercropped with soybeans and onions or soybeans and garlic.

Weeding

In order to maintain the satisfactory development of roots, about two weeding are necessary during the monsoon and one hoeing at the end of the growing season (December). This may be done in large plantations using a tractor-drawn cultivator which is cheaper than manual labor. Hoeing by means of a tractor-drawn wheel-hoe is the most economical.

Disease

Leaf spot caused by *Cercospora rauwolfia* manifests as dark-brown colored spots on the upper surface of the leaf and yellowish-brown on lower surface. Dithane Z-78 or M-45 (0.2%) is to be sprayed in early June with a monthly interval until November; *Alternaria tenuis may* cause minute, brownish or dark-colored circular spots with a yellowish margin on ventral side of leaves, and spray of watery solution of Blitox (3/l) is suggested as remedy; mosaic disease may be avoided by proper selection of the germplasms (Shetty et al. 2014; Paturkar and Khobragade 2016).

For the control of root knots or galls of various sizes associated with stunted growth, etiolation and decrease in leaf size are due to the presence of mites, various soil fungi and nematodes (*Heterodera* sp.), especially in brown clay soils (but not dark clay soils), application of 25 kg of 3G Carbofuran or 20 kg of 10G Phorate granules/hectare is recommended; and for the control of pyralid caterpillar (*Glyphodes vertumnalis*) or some other caterpillars (*Daphnis nerii*, *Deilophola nerii*), 0.2% Rogor spray is suggested; mixing of phorate granules with the soil at the time of nursery preparation is recommended to check attack of Cockchafer and Haygrubs.

The other diseases reported include target leaf spot caused by *Coryneospora cassicola* and *Pellicularia filamentosa*, leaf-blotch caused by *Cercospora serpentina*, anthracnose caused by *Collitotrichum gloeosporoides*, die back caused by *Collitotrichum dematium*, powdery mildew caused by *Leviellula taurica* and fusarium wilt (*Fusarium oxysporum*, *F. rauvolfii*). The root-knot nematode (*Meloidogyne* spp.) is also reported on this crop.

This medicinal plant, however, can be grown without chemical pesticides using biopesticides prepared (either single or mixture) from neem (kernel, seeds, and leaves), Chitrakmool (*Plumbaga zeylanica*), Dhatura, cattle urine, etc. However, following measures have been reported to control different diseases.

Harvesting and processing

Maturity period is 3 years when the subaerial parts become dry and main root reach a depth of 0.9 m. However, roots of exploitable size are generally collected 2–3 years after planting or from 18 months onward. It is reported that roots dug out in December (winter) when the plants have shed their leaves are richer in total content of alkaloids than the roots harvested in August (summer). However, root yields at different age and season have showed that 18 months duration crop produce maximum root yield. Transplanting is done in July, and the harvesting period coincides with the shedding of leaves during early autumn season next year. At this stage, the roots contain maximum concretion of total alkaloids. At harvest, the root may be found to go up to 40 cm deep in the soil. Harvesting is done by digging up the roots, and thin roots are also collected. A light irrigation should be given in advance to facilitate easy digging of roots. The roots may be dug out carefully from the subsoil, manually or by using a board plow. After digging the roots are cleaned, washed, and cut into 12–15-cm pieces for convenience in drying and storage. The dry roots (air dried) till they become brittle possess up to 8–10% of moisture. The dried roots are stored in polythene lined gunny bags in cool dry place to protect it from mold. Care should be taken to keep the root bark intact as the bark constitutes 40–56% of the whole root and has a higher alkaloid content. Under the present system, only taproots are selected for processing. It has been observed the rootlets are also rich in alkaloids, so these should be included in the material.

Average Yield

Optimum yield of roots (including thick, thin, and fibrous) is obtained when the propagation is done by seeds. The yield of fresh roots per plant varies widely from 0.1 to 4 kg, the total yield of air dry roots in the case of plants per hectare raised from seeds and stem cuttings was estimated to be about 1175 and 1750 kg, respectively. On an average, root yield varies from 1500 to 2500 kg dry root per hectare under irrigation depending upon soil fertility, crop stand, and management. Some cultivators report that the average yield is 2700–3300 kg dry roots and 8–10 kg seed per hectare from a 2- and 3-year-old plantation under irrigated conditions on sandy, clay-loam soil. Soil NPK level, especially the nitrogen level, positively influences growth and alkaloid level in different medicinal plants including *Rauvolfia* (Alamgir et al. 1999).

(ii) Cultivation *Senna*

Senna (*Cassia* spp. of Caesalpiniaceae) is a valuable plant drug in Ayurveda and modern system of medicine for the treatment of constipation. It is a acidophilus helophyte. Senna is a small perennial shrub of less than a meter in height ascending branches. The leaves are compound pinnate, petiolate about 10 cm long, and bear 5–8 pairs of leaflets each on a small stalk. Cultivation of Senna does not require

much expenditure on irrigation, manuring, pesticides, protection, and other pre- and post-harvest care.

Senna is native to Yemen, South Arabia, and Egypt. *Cassia angustifolia* Vahl. is now naturalized and cultivated in some parts of Tamil Nadu, Bangalore, Gujarat, and Delhi in India. India is the main producer of this crop in the world and exports Senna leaves and pods worth over Indian currency 6 million annually. Leaves and pods are the usable parts in which they contain sennoside, the laxative principle extensively used as a laxative in medicine.

Soil and Climate

The crop can thrive on a variety of soils from sandy red loams to alluvial loams. The average pH ranges from 7 to 8.5. It is very sensitive to water-logging and hence requires well-drained soils. Senna is a warmth loving crop (18.30 °C), requires bright sunshine for its successful growth and can be grown as an early summer (February–March) or a winter (October–November) crop. Heavy rains and cloudy weather during growth are harmful to the crop. An average rainfall of 25–40 cm that distributed from June to October is sufficient to produce good crop.

Land preparation

The land is plowed deep, and the soil is exposed to sun for 110–115 days to dry out roots of perennial weeds followed by two cross plowing harrowing and leveling. FYM is incorporated into the soil at the time of final cross plowing. Then, the land is laid out into plots of convenient size with irrigation channels.

Seed sowing and fertilization

The crop is raised by seeds. The seeds have hard and tough seed coat. Soaking seeds for 10–12 h before sowing was reported to give 100% germination. Senna is grown as a pure crop as well as a mixed crop with gram, ginger, chilies, and cotton. Generally, two sowing seasons are recognized, i.e., February to March (irrigated crop) and November (rainfed crop). The seed rate is 27 kg per hectare under rainfed conditions and 15 kg per hectare for the irrigated crop. The seeds are broadcast or preferably sown at 30 cm lines to 30 cm apart and 1.5–2.5 cm depth in a well prepared land. Germination commences on third day and completed within a fortnight. Before sowing the seeds, the field should be perfectly leveled otherwise it hampers the uniform seed germination. It is found that the seed treatment with Thiram, Captain or Agroson G. N. at 2.5 g/kg protect the seedlings from damping-off and seedling blight diseases which are very common. The application of 20 kg of N and 40 kg of P per hectare at planting, supplemented with 40–60 kg/ha of N in 3 split doses is preferred.

Thinning and weeding

The first weeding cum hoeing is done at 25–30 days of sowing, a second at 75–80 days and a third at 110 days to keep the crop free from weeds. It flowers in about 2 months after sowing and the first flush of flowering stalks is removed to induce a higher degree of branching. Use of Treflan herbicide as pre-emergent spray at the rate of 4 kg/ha has been reported to increase the yield and anthraquinone content.

Manures, Fertilizers and Pesticides
The medicinal plants have to be grown without chemical fertilizers and use of pesticides. Organic manures like, FYM, vermi-compost, green manure, etc., may be used as per requirement of the species. To prevent diseases, biopesticides could be prepared (either single or mixture) from neem (kernel, seeds, and leaves), Chitrakmool, Dhatura, cow urine, etc.

Irrigation
Senna could be economically grown under rainfed conditions. In most years, the crop needs no irrigations except under the conditions of prolonged drought. However, when it is grown as a semi-irrigated crop, the yield increased considerably. About 5–8 light irrigations are enough to raise a good crop of Senna; however, heavy irrigations are injurious to the crop.

Plant Protection
Damping-off is common in the seedling stage. To control the disease, seed treatment with fungicides, e.g., Captain, is recommended. The pods are attacked by a borer during storage, leading to considerable damage.

Harvest and Post-harvest Operation
Senna plant produces foliage containing higher sennosides between 5 and 90 days age, depending upon the total plant growth. The picking of leaves starts in early May when leaves are fully grown, thick, and bluish, and the picking of leaves is done by hand so that most of the growing tops are removed at harvest. This also induces the plants to produce more of branching which otherwise reduce foliage growth considerably. A second picking is taken at 90–100 days and the third harvest between 130 and 150 days when picking of leaves is taken along with the plucking of pods followed by the uprooting of entire plants during August or April–May, and the harvested material includes both leaves and pods together. The pods are harvested a little before maturity to maintain their green color. The leaves and the pods are dried in a thin layer in shade for 4–7 days to reduce moisture level; the pods are lightly beaten during drying to remove the interseed material. Further drying is done in well-ventilated drying sheds that takes 10–12 days to dry completely. The dried leaves and pods should have light green to greenish yellow color. A rapid mechanical drying at 40 °C could also be attempted. The careless drying of the harvested crop spoils the color and lowers its active content. The produce is graded, baled under hydraulic pressure, and wrapped in gunny bags, for long-distance transport or for export.

Yield
A good average crop of Senna can give 15 quintals of dry leaves and 7 quintals of pods per hectare under irrigated and good management conditions. The yield under rainfed conditions is about 10 quintals of leaves and 4 quintals of pods. The produce should contain about 2.5% of active principles, calculated as anthraquinones. Alamgir et al. (2004) reported the increased level of biomass and secondary metabolites production in different members of the Archichlamydeae under rich NPK fertilization.

(iii) Cultivation of *Atropa belladonna*

Belladonna (*A. belladonna* L. of Solanaceae) is European species, presently grown on a small scale in Kashmir, India. The plant is a small perennial herb which grows up to 1.5 m in height. It branched freely and produces a large tapering root. The leaves and roots of belladonna constitute the commercial drug which contains atropine, hyoscyamine. and hyoscine, used in pharmacy for their mydriatic, analgesic, and antispasmodic properties; the roots are used for external application only. The leaves and roots should contain not less than 0.3 and 0.4% of the total alkaloids calculated as hyoscyamine. *A. acuminata* Royel is a closely related Indian species, found at altitudes between 1800 and 3000 m in the western Himalayas; its leaves and roots contain similar alkaloids. A part of belladonna alkaloids and their products used in India is imported.

Climate

The crop prefers a well-drained slightly acidic, silty-loam to clayey-loam soil, rich in humus. It cannot stand water-logged conditions. It is a crop of the temperate climate prefers a sunny location and clear weather, particularly preceding and during the harvesting of the crop; continuous dampness or high humidity favors root rot.

Development of Seedlings in Nursery Bed

The crop shows a wide variation in growth and alkaloid content in its plants population. Seeds from selected plants with high alkaloid contents should be used for raising a plantation. Propagation through seed is the easiest and least expensive method, although vegetative methods, such as shoot, root, and root–shoot cuttings are also used. The seeds are very small, weighing about 700 per g. They should be treated with ethyl alcohol for 3 min or with petroleum either for 6 min for improving germination. The treated seeds should be washed in running water for a few hours to remove the adhering chemicals. The seeds are sown in rows in the nursery bed during early spring. Germination takes place within 10–21 days and is 15–40%. Therefore, 4 kg of seed gives enough seedlings to plants in one hectare.

Transplantation

The seedling bearing 1–3 leaves is planted in the field during August at 45 × 60 cm or 60 × 60 cm spacing. Ridge planting is preferred in localities receiving heavy monsoon rains.

Fertilization, Irrigation, and Management

The land is given about 40 tonnes of farmyard manure, besides 100 kg of diammonium phosphate and 30 g of K_2O per hectare before planting, and 20 kg of N is given at the time of branching and each time the crop is picked. The crop is irrigated after every 10–15 days during summer. The plantation is given to 2–3 weddings and hoeings before the first leaf crop is obtained and then one or two hoeings are usually given before each leaf picking.

Plant Protection

Cutworms (*Agrotis flammatra*) attack the tender growing seedling during yearly summer. The application of 5% Aldrin dust at 20–25 g/m^2 of the nursery bed before sowing protects the crop. The beds may be drenched with 1:19 wettable solutions of chlordane, 2–3 times after every 10 days during the attack of the pace. Sometimes damping-off of seedlings is caused by Pythium sp., and chloropicrin is recommended as a fumigant. Root rot also damages the crop; the affected plants along with the adhering soil are removed and burnt. Seeds treated with the Agrosan generally protect the seedlings from soil-borne diseases.

Harvest and Post-harvest Management

The first picking of leaves is obtained in October; in subsequent years, 3–4 leaf crops are obtained for the next three years. Harvesting is done on bright sunny days by cutting the plants 20–25 cm above the ground, except at the time of the autumn harvest when the plants are cut 3 cm above the ground. The stumps put forth fresh growth during the succeeding spring and bear flowers during June–August, and the berries are produced in October. The alkaloids are synthesized in the root and are translocated through the stem to the leaves.

The harvested crop is dried rapidly in the sun for 2–3 days, and the leafstalks are detached only after the produce is dried. The plants are uprooted after three or four years; the thicker are sliced into 3–4-cm-long pieces and dried. The crop loses 70–80% of its weight during drying. A well-dried leaf crop retains its green color.

Yield

The average crop yield in the first year is 300 kg of leaves and thereafter, 750 kg of leaves per hectare annually. An additional root crop of 200–300 kg per hectare is obtained when the plants are finally uprooted. Higher average yield of 1–1.2 tonnes per hectare is reported from European countries. The produce should be stored in cool dry place away from light.

(iv) Cultivation of *Catharanthus roseus*

C. roseus, commonly known as the Madagascar periwinkle, is native and endemic to Madagascar. It is naturalized in subtropical and tropical areas of the world. Numerous cultivars are known for variation in flower color (white, mauve, peach, scarlet, and reddish orange), and also for tolerance of cooler growing conditions in temperate regions. It thrives in hot and humid environments, in full sun or partial shade and flowers all year round in hot climates. But it is sensitive to over-watering and cannot withstand frosts (not below 5–7 °C). It is best grown indoors in temperate climates. In the wild, plant is an endangered species mainly due to habitat destruction by slash and burn agriculture.

Madagascar periwinkle is widely cultivated for herbal medicine and as an ornamental plant. It is easy to cultivate and can be easily propagated by seed or by apical semi-ripe cuttings in light, free-draining compost. The best results are obtained when bottom heat and high humidity are provided. Seeds set for germination should be maintained at 22–25 °C in the dark until the seeds germinate. Full sun and well-drained soil are preferred and because of its hardiness, and it can

tolerate dry and nutritionally deficient conditions. It is noted for its long-flowering period, throughout the year in tropical conditions, and from spring to late autumn, in warm-temperate climates.

It is an oral poison, but in Ayurveda and Traditional Chinese Medicine (TCM), the extracts of roots and shoots are used against several diseases, including diabetes, malaria, and Hodgkin's lymphoma. The alkaloids vinblastine and vincristine extracted from the plant are used in the treatment of leukemia and Hodgkin's lymphoma in modern medicine.

9.2 Biotechnology and In Vitro Production of Secondary Metabolites

The cultivation of medicinal plants at field level often becomes problematic due to following reasons:

(i) Field production is dependent on season and climate and affected by diseases and pests;
(ii) Natural sources are becoming extremely scarce;
(iii) There may be technical and economic problems in production;
(iv) Production is labor intensive and therefore costly;
(v) Political instability in the country of production; and
(vi) Diplomatic relation with the country of origin.

The above problems have led to make a new approach to get drug substances through biotechnological means from cell, tissue, and organ cultures of medicinal plants.

Advantages of Biotechnology

Biotechnologists have special interest in plant cell tissue and organ cultures for the large-scale production of commercially important compounds including pharmaceuticals, flavors, fragrances, cosmetics, food additives, feedstocks, and antimicrobials. The advantages of biotechnology for the production of industrially important secondary metabolic compounds over the field level of medicinal plants for active drug principles include the following:

(i) Plant cell cultures are independent from environmental factors, seasonal variations, pest and microbial diseases, and geographical constraints as well as political interference;
(ii) Compounds can be produced under controlled conditions as per market demands;
(iii) Cell growth can be controlled to facilitate improved product formation, a more consistent product quality and yield can be maintained;
(iv) New routes of synthesis can be recovered from mutant cell lines which may lead to the development of novel products of commercial importance, which are not normally found in plants;

(v) Culture of cells will reduce the pressure on already over-exploited medicinal and other economically important plants as well as the production time is less and labor costs are minimal;
(vi) Plant cell tissue and cultures are particularly useful in case of plants which are difficult or expensive to be grown in the fields; and
(vii) Many of the commercially high valuable chemicals may be produced including drugs, flavors, perfumes, pigments, and agrochemicals.
(viii) Biotransformation reactions (converting specific substrates to valuable products) can be carried out with certain cultured cells.

Tissue culture production of useful secondary metabolites is cheaper compared to synthetic production, and at present, about 25–30% of medicines for human use and the various chemical materials for industrial purposes are obtained from plant tissue cultures.

Disadvantages of Biotechnology

(i) In general, in vitro production of secondary metabolites is lower when compared to intact plants;
(ii) Many a times, secondary metabolites are formed in differentiated tissues or organs and in such cases, non-differentiated culture cells (callus) can produce little;
(iii) Cultured cells are genetically unstable and may undergo mutation and under such circumstances, the production of secondary metabolite may be drastically reduced, as the culture ages;
(iv) Vigorous stirring is necessary to prevent aggregation of cultured cells, and this may often lead to cell damage; and
(v) Strict aseptic conditions have to be maintained during culture technique, and any infection to the culture may severely affect product formation.

9.2.1 Principles of Biotechnology and Laboratory Techniques

Biotechnology is the use of living systems and organisms to develop or make useful products or any technological application that uses biological systems, living organisms, or derivatives thereof, to make or modify products or processes for specific use. Similar to biotechnology, plant biotechnology may be defined as generation of useful products or services from plant cells, tissues and, often, organs (very small organ explants). Such cells, tissues, and organs are either continuously maintained in vitro or they pass through a variable phase to enable regeneration from them of complete plants which are ultimately transferred to the field.

Research in the area of plant tissue and organ culture technology has resulted in the production of many bioactive metabolites (alkaloids, terpenoids, steroids, saponins, phenolics, flavonoids, and amino acids, etc.) for new therapeutics under defined conditions; however, there are some inherent limitations including low yield of bioactive metabolites. Recombinant DNA techniques can be used to manipulate metabolic pathways for high yield and to produce protein pharmaceuticals such as antibodies, and protein hormones. The new disciplines of bioinformatics and genomics can find application in drug discovery from plant-based products, and biotechnological procedures can enhance and advance the studies of medicinal plants. Therefore, in vitro culture of plant cell, tissue and organs form an integral part of any plant biotechnology activity.

The various objectives achieved by plant biotechnology may be summarized as follows:

(i) Useful biochemical production (large-scale cell cultures); (ii) Rapid clonal multiplication (e.g., adventitious shoot/bulb/protocorm); (iii) Virus elimination (e.g., thermo-, cryo-, or chemo-therapy coupled with meristem culture); (iv) Rapid development of homozygous lines by producing haploids (e.g., anther culture, ovary culture, interspecific hybridization); (v) Production/recovery of difficult to produce hybrids (e.g., embryo rescue, in vitro pollination); (vi) Germplasm conservation of vegetatively reproducing plants or those producing recalcitrant seeds (cryopreservation, slow growth cultures, DNA clones); (vii) Genetic modification of plants (e.g., somaclonal variation, somatic hybridization, cybridization, and gene transfer), and (viii) Creation of genome maps and use of molecular markers to assist conventional breeding efforts.

The secondary metabolite production process comprises of several aspects including (i) selection of cell lines for high yield of secondary metabolites, (ii) large-scale cultivation of plant cells, (iii) medium composition and effect of nutrients, (iv) elicitor-induced production of secondary metabolites, (v) effect of environmental factors, (vi) biotransformation using plant cell cultures, and (vii) secondary metabolite release and analysis.

Culture Media and Other Factors for Optimum Production of Secondary Metabolites

A wide variety of culture media is available, and the choice of culture media is dependent on the purpose and requirements of the experiment. Selection of appropriate growth medium is important for the in vitro cultivation of cell tissue and organ. A culture medium is a liquid or gel designed to support the growth of the selected explants. It generally contains of an appropriate source of energy, structural material, growth factors, etc., which support and regulate the metabolic activities and also cell cycle. A typical culture medium is composed of a complement of amino acids (nitrogen source), vitamins, hormones (growth factors), inorganic salts, glucose (carbon and energy source), elicitors, and attachment factors. In addition to nutrients, the medium also helps maintain pH and osmolality. Most commonly used

culture media include White's medium, Murashige and Skoog (MS) medium, Gamborg or B5 medium, Chu or N6 medium, Nitsch's medium, etc., are some common media used for cell tissue culture from different explant sources and Eagle's minimum essential medium (EMEM), Dulbecco's modified Eagle's medium (DMEM), RPMI-1640 (developed at Roswell Park Memorial Institute, RPMI, in Buffalo, New York), Ham's nutrient mixtures, etc., for some of the widely used media used for animal cell culture.

(i) Media Components

One of the most important factors governing the growth and morphogenesis of plant tissues in culture is the composition of the culture medium. The basic nutrient requirements of cultured plant cells are very similar to those of whole plants. Plant tissue and cell culture media are generally made up of some or all of the following components: macronutrients, micronutrients, vitamins, amino acids, or other nitrogen supplements, sugar(s), other undefined organic supplements, solidifying agents or support systems, and growth regulators. Several media formulations are commonly used for the majority of all cell and tissue culture work. These media formulations include those described by White, Murashige and Skoog, Gamborg et al., Schenk and Hilderbrandt, Nitsch and Nitsch, and Lloyd and McCown. Murashige and Skoog's MS medium, Schenk and Hildebrand's SH medium, and Gamborg's B-5 medium are all high in macronutrients, while the other media formulations contain considerably less of the macronutrients.

(ii) Macronutrients

The macronutrients provide the six major elements: nitrogen (N), phosphorus (P), potassium (K), calcium (Ca), magnesium (Mg), and sulfur (S), required for plant cell or tissue growth. The optimum concentration of each nutrient for achieving maximum growth rates varies considerably among species. Culture media should contain at least 25–60 mM of inorganic nitrogen for adequate plant cell growth. Plant cells may grow on nitrates alone, but considerably better results are obtained when the medium contains both a nitrate and ammonium nitrogen source. Certain species require ammonium or another source of reduced nitrogen for cell growth to occur. Nitrates are usually supplied in the range of 25–20 mM; typical ammonium concentrations range between 2 and 20 mM. However, ammonium concentrations in excess of 8 mM may be deleterious to cell growth of certain species. Cells can grow on a culture medium containing ammonium as the sole nitrogen source if one or more of the TCA cycle acids (e.g., citrate, succinate, or malate) are also included in the culture medium at concentrations of approximately 10 mM. When nitrate and ammonium sources of nitrogen are utilized together in the culture medium, the ammonium ions will be utilized together in the culture medium, the ammonium ions will be utilized more rapidly and before the nitrate ions. Potassium is required for cell growth of most plant species. Most media contain K, in the nitrate or chloride form, at concentrations of 20–30 mM. The optimum concentrations of P, Mg, S, and Ca range from 1 to 3 mM when all other requirements for cell growth

are satisfied. Higher concentrations of these nutrients may be required if deficiencies in other nutrients exist.

(iii) Micronutrients

The essential micronutrients for plant cell and tissue growth include iron (Fe), manganese (Mn), zinc (Zn), boron (B), copper (Cu), and molybdenum (Mo). Chelated forms of iron and zinc are commonly used in preparing culture media. Iron may be the most critical of all the micronutrients. Iron citrate and tartrate may be used in culture media, but these compounds are difficult to dissolve and frequently precipitate after media are prepared. Murashige and Skoog used an ethylene diaminetetraacetic acid (EDTA)-iron chelate to bypass this problem. Cobalt (Co) and iodine (I) may also be added to certain media, but strict cell growth requirements for these elements have not been established. Sodium (Na) and chlorine (Cl) are also used in some media but are not essential for cell growth. Copper and Cobalt are normally added to culture media at concentrations of 0.1 μM, Fe and Mo at 1 μM, I at 5 μM, Zn at 5–30 μM, Mn at 20–90 μM, and B at 25–100 μM.

(iv) Carbon and energy source

The preferred carbohydrate in plant cell culture media is sucrose. Glucose and fructose may be substituted in some cases, glucose being as effective as sucrose and fructose being somewhat less effective. Other carbohydrates that have been tested include lactose, galactose, raffinose, maltose, and starch. Sucrose concentrations of culture media normally range between 2 and 3%. Use of autoclaved fructose can be detrimental to cell growth. Carbohydrates must be supplied to the culture medium because few plant cell lines have been isolated that are fully autotrophic, e.g., capable of supplying their own carbohydrate needs by CO_2 assimilation during photosynthesis.

(v) Vitamins

Normal plants synthesize the vitamins required for their growth and development. Vitamins are required by plants as catalysts in various metabolic processes. When plant cells and tissues are grown in vitro, some vitamins may become limiting factors for cell growth. The vitamins most frequently used in cell and tissue culture media include thiamin (B1), nicotinic acid, pyridoxine (B6), and myo-inositol. Thiamin is the one vitamin that is basically required by all cells for growth. Thiamin is normally used at concentrations ranging from 0.1 to 10.0 mg/l. Nicotinic acid and pyridoxine are often added to culture media but are not essential for cell growth in many species. Nicotinic acid is normally used at concentrations of 0.1–5.0 mg/l; pyridoxine is used at 0.1–10.0 mg/l. Myo-inositol is commonly included in many vitamin stock solutions. Although it is a carbohydrate not a vitamin, it has been shown to stimulate growth in certain cell cultures. Its presence in the culture medium is not essential, but in small quantities myo-inositol stimulates cell growth in most species. Myo-inositol is generally used in plant cell and tissue culture media at concentrations of 50–5000 mg/l.

Other vitamins such as biotin, folic acid, ascorbic acid, pantothenic acid, vitamin E (tocopherol), riboflavin, and *p*-aminobenzoic acid have been included in some cell culture media. The requirement for these vitamins by plant cell cultures is generally negligible, and they are not considered growth-limiting factors. These vitamins are generally added to the culture medium only when the concentration of thiamin is below the desired level or when it is desirable to grow cells at very low population densities.

(vi) Amino acids or other nitrogen supplements

Although cultured cells are normally capable of synthesizing all of the required amino acids, the addition of certain amino acids or amino acid mixtures may be used to further stimulate cell growth. The use of amino acids is particularly important for establishing cell cultures and protoplast cultures. Amino acids provide plant cells with an immediately available source of nitrogen, which generally can be taken up by the cells more rapidly than inorganic nitrogen. The most common sources of organic nitrogen used in culture media are amino acid mixtures (e.g., casein hydrolysate), L-glutamine, L-asparagine, and adenine. Casein hydrolysate is generally used at concentrations between 0.05 and 0.1%. When amino acids are added alone, care must be taken, as they can be inhibitory to cell growth. Examples of amino acids included in culture media to enhance cell growth are glycine at 2 mg/l, glutamine up to 8 mM, asparagine at 100 mg/l, L-arginine and cysteine at 10 mg/l, and L-tyrosine at 100 mg/l. Tyrosine has been used to stimulate morphogenesis in cell cultures but should only be used in an agar medium. Supplementation of the culture medium with adenine sulfate can stimulate cell growth and greatly enhance shoot formation.

(viii) Undefined organic supplements

Addition of a wide variety of organic extracts to culture media often results in favorable tissue responses. Supplements that have been tested include protein hydrolysates, coconut milk, yeast extracts, malt extracts, ground banana, orange juice, and tomato juice. However, undefined organic supplements should only be used as a last resort, and only coconut milk and protein hydrolysates are used to any extent today. Protein (casein) hydrolysates are generally added to culture media at a concentration of 0.05–0.1%, while coconut milk is commonly used at 5–20% (v/v). The addition of activated charcoal (AC) to culture media may have a beneficial effect. The effect of AC is generally attributed to one of three factors: absorption of inhibitory compounds, absorption of growth regulators from the culture medium, or darkening of the medium. The inhibition of growth in the presence of AC is generally attributed to the absorption of phytohormones to AC. 1-Napthaleneacetic acid (NAA), kinetin, 6-benzylaminopurine (BAP), indole-3-acetic acid (IAA), and 6-γ-γ-dimethylallylaminopurine (2iP) all bind to AC, with the latter two growth regulators binding quite rapidly. The stimulation of cell growth by AC is generally attributed to its ability to bind to toxic phenolic compounds produced during

culture. Activated charcoal is generally acid-washed prior to addition to the culture medium at a concentration of 0.5–3.0%.

(ix) Solidifying agents or support systems

Agar is the most commonly used gelling agent for preparing semisolid and solid plant tissue culture media. Agar has several advantages over other gelling agents. First, when agar is mixed with water, it forms a gel that melts at approximately 60–100 °C and solidifies at approximately 45 °C; thus, agar gels are stable at all feasible incubation temperatures. Additionally, agar gels do not react with media constituents and are not digested by plant enzymes. The firmness of an agar gel is controlled by the concentration and brand of agar used in the culture medium and the pH of the medium. The agar concentrations commonly used in plant cell culture media range between 0.5 and 1.0%; these concentrations give a firm gel at the pH's typical of plant cell culture media. Another gelling agent commonly used for commercial as well as research purposes is Gelrite. This product is synthetic and should be used at 1.25–2.5 g/l, resulting in a clear gel which aids in detecting contamination. Alternative methods of support have included use of perforated cellophane, filter paper bridges, filter paper wicks, polyurethane foam, and polyester fleece. Whether explants grow best on agar or on other supporting agents varies from one species of plant to the next.

Growth Regulators

Four broad classes of growth regulators are important in plant tissue culture; the auxins, cytokinins, gibberellins, and abscisic acid. Skoog and Miller were the first to report that the ration of auxin to cytokinin determined the type and extent of organogenesis in plant cell cultures. Both an auxin and cytokinin are usually added to culture media in order to obtain morphogenesis, although the ratio of hormones required for root and shoot induction is not universally the same. Considerable variability exists among genera, species, and even cultivars in the type and amount of auxin and cytokinin required for induction of morphogenesis. The auxins commonly used in plant tissue culture media are 1H-indole-3-acetic acid (IAA), 1H-indole-3-butyric acid (IBA), (2,4-dichlorophenoxy) acetic acid (2,4-D), and 1-napthaleneacetic acid (NAA). The only naturally occurring auxin found in plant tissues is IAA. Other synthetic auxins that have been used in plant cell culture include 4-chlorophenoxyacetic acid or *p*-chlorophenoxyacetic acid (4-CPA, PCPA), (2,4,5-trichlorophenoxy)acetic acid (2,4,5-T), 3,6-dichloro-2-methoxybenzoic acid (Dicamba), and 4-amino-3,5,6-trichloropicolinic acid (Picloram). The various auxins differ in their physiological activity and in the extent to which they move through tissue, are bound to the cells, or metabolized. Naturally occurring IAA has been shown to have less physiological activity than synthetic auxins. Based on stem curvature assays, 2,4-D has eight to twelve times the activity, 2,4,5-T has four times the activity, PCPA and Picloram have two to four times the activity, and NAA has two times the activity of IAA. Although 2,4-D, 2,4,5-T, PCPA, and Picloram are often used to induce rapid cell proliferation, exposure to high levels or prolonged exposure to these auxins, particularly 2,4-D, results in suppressed morphogenetic

activity. Auxins are generally included in a culture medium to stimulate callus production and cell growth, to initiate shoots, particularly roots, and to induce somatic embryogenesis and stimulate growth from shoot apices and shoot tip cultures. The cytokinins commonly used in the culture media include 6-benzylaminopurine or 6-benzyladenine (BAP, BA), 6-γ-γ-dimethylaminopurine (2iP), *N*-(2-furanylmethyl)-1H-purine-6-amine (kinetin), and 6-(4-hydroxy-3-methyl-trans-2-butenylamino)purine (zeatin). Zeatin and 2iP are considered to be naturally occurring cytokinins, while BA and kinetin are synthetically derived cytokinins. Adenine, another naturally occurring compound, has a base structure similar to that of the cytokinins and has shown cytokinin-like activity in some cases. Many plant tissues have an absolute requirement for a specific cytokinin for morphogenesis to occur, whereas some tissues are considered to be cytokinin independent, i.e., no cytokinin or a specific cytokinin may be required for organogenesis. The cytokinins are generally added to a culture medium to stimulate cell division, to induce shoot formation and axillary shoot proliferation, and to inhibit root formation. The type of morphogenesis that occurs in a plant tissue culture largely depends upon the ratio and concentrations of auxins and cytokinins present in the medium. Root initiation of plantlets, embryogenesis, and callus initiation all generally occur when the ration of auxin to cytokinin is high, whereas adventitious and axillary shoot proliferation occurs when the ration is low. The concentrations of auxins and cytokinins are equally as important as their ratio. Gibberellins (GA3) and abscisic acid (ABA) are two other growth regulators occasionally used in culture media. Plant tissue cultures can usually be induced to grow without either GA3 or ABA, although, certain species may require these hormones for enhanced growth. Generally, GA3 is added to culture media to promote the growth of low-density cell cultures, to enhance callus growth, and to elongate dwarfed or stunted plantlets. Abscisic acid is generally added to culture media to either inhibit or stimulate callus growth (depending upon the species), to enhance, inhibit, or stimulate callus growth (depending upon the species), to enhance shoot or bud proliferation, and to inhibit latter stages of embryo development.

Preparation of Stock Solutions

The use of stock solutions reduces the number of repetitive operations involved in media preparation and, hence, the chance of human or experimental error. Moreover, direct weighing of media components (e.g., micronutrients and hormones) that are required only in milligram or microgram quantities in the final formulation cannot be performed with sufficient accuracy for tissue culture work. For these components, preparation of concentrated stock solutions and subsequent dilution into the final media is standard procedure. In addition, concentrated solutions of some materials are more stable and can be stored for longer periods than more dilute solutions. To prepare a stock solution, weigh out the required amount of the compound and place it in a clean flask. It is common practice to make a stock solution 10× or 100×, depending upon the solubility of the compound. Once the chemical is in the flask, dissolve it in a small amount of water, ethyl

alcohol, 1 N NaOH, or 1 N HCL. Next, slowly add double-distilled water to the flask, while agitating. Continue this until the proper volume is reached. Label the flask with the name of the solution, preparation and expiration dates, and the name of the person who prepared the solution. Certain items, e.g., IAA, must be prepared and stored in amber bottles to prevent photodecomposition.

Macronutrients in Stock Solutions

Stock solutions of macronutrients can be prepared at 10 times the concentration of the final medium. A separate stock solution for calcium salts may be required to prevent precipitation. Stock solution of macronutrients can be stored safely for several weeks in a refrigerator at 2–4 °C.

Micronutrients in stock solutions

Micronutrient stock solutions are generally made up at 100 times their final strength. It is recommended that micronutrient stocks be stored in either a refrigerator or freezer until needed. Micronutrient stock solutions could be stored in a refrigerator for up to 1 year without appreciable deterioration. Iron stock solutions should be prepared and stored separately from other micronutrients in an amber storage bottle. Formulations for preparing stock solutions of iron are presented later.

Vitamins in stock solutions

Vitamins are prepared as 100× or 1000× stock solutions and stored in a freezer (−20 °C) until used. Vitamin stock solutions should be made up each time media is prepared if a refrigerator or freezer is not available. Vitamin stock solutions should be made up each time media is prepared if a refrigerator or freezer is not available. Vitamin stock solutions can be stored safely in a refrigerator for 2–3 months but should be discarded after that time.

Growth Regulators

The auxins NAA and 2,4-D are considered to be stable and can be stored at 4 °C for several months; IAA should be stored at −20 °C. Auxin stock solutions are generally prepared at 100–1000 times the final desired concentrations. Solution of NAA and 2,4-D can be stored for several months in a refriger at or indefinitely at −20 °C. Generally, IAA and 2,4-D are dissolved in a small volume of 95% ethyl alcohol or KOH and then brought to volume with double-distilled water; NAA can be dissolved in a small amount of 1 N NaOH or KOH, which also can be used to dissolve 2,4-D and IAA. The cytokinins are considered to be stable and can be stored at −20 °C. Cytokinin stock solutions are generally prepared at 100× to 1000× concentrations. Many of the cytokinins are difficult to dissolve, and a few drops of either 1 N HCL, 1 N NaOH, in KOH or DMSO, is required to bring them into solution.

Storage of Stock Solutions

Storage conditions for most stock solutions have already been pointed out; however, some additional points can be made. For convenience, many laboratories prepare stock solutions and then divide them into aliquots sufficient to prepare from 1 to 10 l of medium; these aliquots are stored in small vials or plastic bags in a

freezer. This procedure removes the inconvenience of having to unthaw a large volume of frozen stock each time medium is prepared. Some have found that heating in a microwave oven is a satisfactory and quick method of thawing concentrated medium (PhytoTechnology Laboratories, Inc. 2003; www.phytotechlab.com).

The medium which limits rapid cell division and early cessation of exponential growth is best for production of secondary metabolites. Growth regulators play an important role in determining the potential productivity of a given culture. For stimulating alkaloid synthesis in suspension culture of *Papaver bracteatum*, IAA has been found to be better than other auxins. At high concentrations, kinetin inhibits the production of alkaloids in *Datura tabula*. In *Solanum aviculare*, reduction in the level of auxin and cytokinin in the medium results in increase of steroid spectrum. Increase in the levels of nitrate, potassium, ammonium, and phosphate supports rapid cell growth but decrease of any of these nutrients limits cell growth and production of secondary metabolites. Increase in sucrose level in the medium increases the yield of secondary metabolites.

(a) Light

Light stimulates biosynthesis of secondary metabolites in cultures. For example, 'cool white' light stimulates biosynthesis of diosgenin in tuber-derived callus and cell suspensions of Dioscorea, solasodine, and solamargine in *Catharanthus roseus* cell cultures.

(b) Temperature

Temperature greatly affects secondary metabolite production in cultures. In Peganum, optimal growth of the callus occurred a 130 °C but maximum alkaloid production was attained at 25 °C. The production of alkaloid decreases at higher temperatures.

(c) Rotation speed of shaker

In tobacco, increase in the rotation speed of shaker (150 r min^{-1}) induces nicotine production, but normal agitation (110 r min^{-1}) results in slight inhibition of nicotine synthesis.

(d) pH of medium

pH of the medium controls the biosynthesis of secondary metabolites. In Ipomoea when cells are cultured at pH 6.3, the production of tryptophol becomes double. The synthesis of tryptophol becomes completely inhibited If pH of the medium drops to 4.8.

9.2.2 *In Vitro Production of Secondary Metabolites*

Medicinal plants constitute a highly potential source for the synthesis of secondary metabolites which are economically important as drugs, flavor and fragrances, dye and pigments, pesticides, and food additives. Plant cells are biosynthetically totipotent, which means that each cell in culture retains complete genetic information and hence is able to produce the range of chemicals found generally in the parent plant. Over 80% of the approximately 30,000 known natural products are of plant origin (Balandrin and Klocke 1988; Fowler and Scragg 1988; Phillipson 1990).

Many of the pharmaceutically important bioactive secondary metabolites are derived from natural sources, and many of them are unique to the plant kingdom and not produced by microbes or animals. Besides, with the help of transgenic technology, it is now possible to modify the cellular biosynthetic routes to produce new bioactive compounds, which were not originally synthesized in plants. Biotechnology offers an opportunity to exploit the cell, tissue, organ, or entire organism by growing them in vitro and to genetically manipulate them to get desired compounds in one hand, and on other, to minimize the extra pressure on arable land (mostly used for food production) for cultivation MAPs. Many facets of biotechnological approaches can be considered and can be used for the production of pharmaceutically important secondary metabolites from plants such as (i) Plant cell tissue and organ cultures (e.g., cell culture, shoot culture, root culture, and scale-up of cultures), (ii) Transgenic plants/organisms (e.g., metabolic engineering, heterologous expression, and molecular farming), (iii) Micropropagation of medicinal plants (e.g., endangered plants, high-yielding varieties, and metabolically engineered plants), (iv) Newer sources (e.g., algae and other photosynthetic marine forms). Recent advances in the molecular biology, enzymology, and fermentation technology suggest that the secondary metabolic plant products can be extracted from the aseptic culture of plant cell, tissue, and organ.

Stockigt et al. (1995) enumerated a number of secondary metabolites that were isolated from tissue and suspension cultures of higher plants including (i) phenylpropanoids (anthocyanins, coumarins, flavonoids, hydroxycinnamoyl derivatives, isoflavonoids, lignans, phenalenones, proanthocyanidins, stilbenes, tannins, etc.); (ii) alkaloids (acridines, betalaines, quinolizidines, furonoquinones, harringtonines, isoquinolines, indoles, purines, pyridines, tropane alkaloids, etc.); (iii) terpenoids (carotenes, monoterpenes, sesquiterpenes, diterpenes, triterpenes, etc.); (iv) quinones (anthroquinones, benzoquinones, naphthoquinones, etc.); and (v) steroids (cardiac glycosides, pregnenolone, etc.). Plant produces innumerable number of secondary metabolites of several categories like (i) flavonoids and allied phenolic and polyphenolic compounds, (ii) terpenoids, (iii) nitrogen-containing alkaloids and sulfur-containing compounds. (Ravishankar and Rao 2000; Rao and Ravishankar 2002; Crozier et al. 2007). The complex structural features of many of the plant-derived compounds are difficult to synthesize. So the synthesis complex bioactive compounds as plants' secondary metabolites paved the way to get desired

Table 9.2 Secondary metabolites produced at higher levels by in vitro plant cell/suspension culture compared to whole plant

Compound	Plant species	Yields (% D.wt.)		Ratio in vitro culture/whole plant	Culture type, C/S[a]
		Tissue culture	Whole plant		
(i) Shikonin	*Lithospermum erythrorhizon*	20	1.5	13.33	S
(ii) Ginsenoside	*Panax ginseng*	27	4.5	6.0	C
(iii) Anthraquinones	*Morinda citrifolia*	18	0.3	60	S
(iv) Ajmalicine	*Catharanthus roseus*	1.0	0.3	3.33	S
(v) Terpentine	*Catharanthus roseus*	1.8	0.5	3.6	C
(vi) Rosmarinic acid	*Coleus blumeii*	15	3	5.0	S
(vii) Ubiquinone-10	*Nicotiana tabacum*	0.036	0.003	12.0	S
(viii) Diosgenin	*Dioscorea deltoides*	2	2	1,0	S
(ix) Benzylisoquinoline alkaloids	*Coptis japonica*	11	5–10	2.2–1.1	S
(x) Berberine	*Thalictrum minor*	10	0.01	1000.0	S
(xi) Berberine	*Coptis japonica*	10	2–4	5–2.5	S
(xii) Anthraquinones	*Galium verum*	5.4	1.2	4.5	S
(xiii) Anthraquinones	*Galium aparine*	3.8	0.2	19.0	S
(xiv) Nicotine	*Nicotiana tabacum*	3.4	2.0	1.7	C
(xv) Glutathione	*Nicotiana tabacum*	5.0	2.1	2.38	C
(xvi) Bisoclaurine	*Stephania cepharantha*	2.3	0.8	2.87	S
(xvii) Tripdiolide	*Tripteryqium wilfordii*	0.05	0.001	50.0	S

[a]*C* Callus culture, *S* Suspension culture

pharmaceuticals, and many of them may now be produced in cell culture in higher proportions compared to whole plant at commercial (Table 9.2).

One of the most exciting aspects of cell culture technology is the potential for producing novel structures not observed in the parent plant, e.g., rutacultin by cultures of *Ruta graveolens* and sesquiterpene lactones by cultures of *A. paniculata*.

Large-scale plant tissue culture is found to be an attractive alternative approach to traditional methods of cultivation of drug plants. Use of liquid medium in suspension cultures allows easy and extensive scaling up by employing bioreactors, although a limited scaling up can be achieved by using larger culture flasks (usually 250-ml flasks containing 50 ml culture medium) or bioreactor—a large volume (1 to >1000 L) culture vessel with provisions for (i) aeration, (ii) stirring to achieve

medium and cell mixing, (iii) contamination control, and (iv) replacement of used medium and/or used medium plus cells.

Plant cell tissue and organ culture

Plant cells are biosynthetically totipotent, each cell in culture retains complete genetic information and hence each cell is able to produce the range of chemicals found generally in the parent plant. Biochemical production by cultured cells can be increased chiefly by the following approaches (i) development of high-producing cultures, (ii) devising a suitable culture medium and conditions, (iii) use of elicitors, and (iv) use of organ cultures.

Strategies for Enhanced Production of Secondary Metabolites in Plant Cell Cultures

Proper Selection of Cell Lines

Development of high-producing clones is a must for high yield of the desired biochemicals. In general, high-producing plants yield high-producing cultures. Therefore, cell cultures must be started from the highest producing plants of the species in question.

Optimization of Medium and Culture Conditions

The constituents of culture medium, like nutrients, phytohormones and also the culture conditions, like temperature, pH, light, inoculum size, etc., influence the production of secondary metabolites. In case of rosamarinic acid, increase of sucrose concentration from 3 to 5%, production increases by five times; IAA enhances the yield of shikonin production, while 2, 4-D and NAA are inhibitory; and NH_4^+ (only 3% of the total N of medium) inhibit shikonin production, while a 30-fold increase in Cu^{2+} concentration caused a threefold increase in shikonin production. Physical factors like white and blue light strongly inhibit shikonin production, while sucrose (5%) is essential for the production of this pigment. It is, therefore, necessary to optimize the factors involved in the regulation of biosynthesis of the desired biochemical by cells in culture.

Addition of Elicitors

Some molecules and physical factors, so-called elicitors, stimulate the production of secondary metabolites in plants or cell culture, and the phenomenon is known as elicitation (induction by applied stresses). Elicitors produced within plant cells are termed as endogenous elicitors, while those produced by microorganisms are called exogenous elicitors. Elicitors of plant origin are cell-wall-derived polysaccharides, e.g., pectin, pectic acid, cellulose, and of microorganism origin are fungal hyphae, carbohydrates, yeast extract, MJ (methyl jasmonate), cell wall components like chitin, chitosan, or glucans; some glycoproteins and low-molecular weight organic acids also cause elicitation. Elicitors of biological origin are called biotic elicitors. Abiotic elicitors are UV, low or high temperature, salts of heavy metals, and

chemicals that disturb membrane integrity. Addition of these elicitors to the medium in low concentration (50–250 mg/1) enhances the production of secondary metabolites. Several abiotic elicitors enhance growth and ginseng saponin biosynthesis in the hairy roots of *Panax ginseng*.

Addition of Precursors

Precursors are the compounds, whether exogenous or endogenous, that can be converted by living system into useful compounds or secondary metabolites. It has been possible to enhance the biosynthesis of specific secondary metabolites by feeding precursors to cell cultures, e.g., amino acids have been added to suspension culture media for production of tropane alkaloids, indole alkaloids. Phenylalanine acts as a precursor of rosmarinic acid; addition of phenylalanine to *Salvia officinalis* suspension cultures stimulated the production of rosmarinic acid and also decreased the production time. Phenylalanine also acts as precursor of the *N*-benzoylphenylisoserine side chain of taxol; supplementation of *Taxus cuspidata* cultures with phenylalanine resulted in increased yields of taxol. The timing of precursor addition is critical for an optimum effect.

Permeabilization

Secondary metabolites produced in cells are often blocked in the vacuole. By manipulating the permeability of cell membrane, they can be secreted out to the media. Permeabilization can be achieved by electric pulse, UV, pressure, sonication, heat, etc. Even charcoal can be added to medium to absorb secondary metabolites.

Immobilization

Cell cultures encapsulated in agarose and calcium alginate gels or entrapped in membranes are called immobilised plant cell cultures. Immobilization of plant cells allows better cell to cell contact and the cells are also protected from high shear stresses. These immobilized systems can effectively increase the productivity of secondary metabolites in a number of species. Elicitors can also be added to these systems to stimulate secondary metabolism.

Procedure for the Production of Secondary Metabolites

The main research program for the production of secondary metabolites from plant cell culture as represented in Fig. 9.1 consists of following essential steps.

Selection of Explant from HYV Plant Species (Cell Line)

At first, the pharmacognosist needs to identify the desired active principles from the test plant. Once it is done, in the next step, investigator needs to screen out the hyper-producing explant that present the most valuable secondary metabolites from the available genetic pool of plants as outlined in Fig. 9.1.

Establishment of In Vitro Cell Lines

After choosing the most promising individual plants, begins the real work of in vitro culture with callus initiation. This work consists mainly in determining the

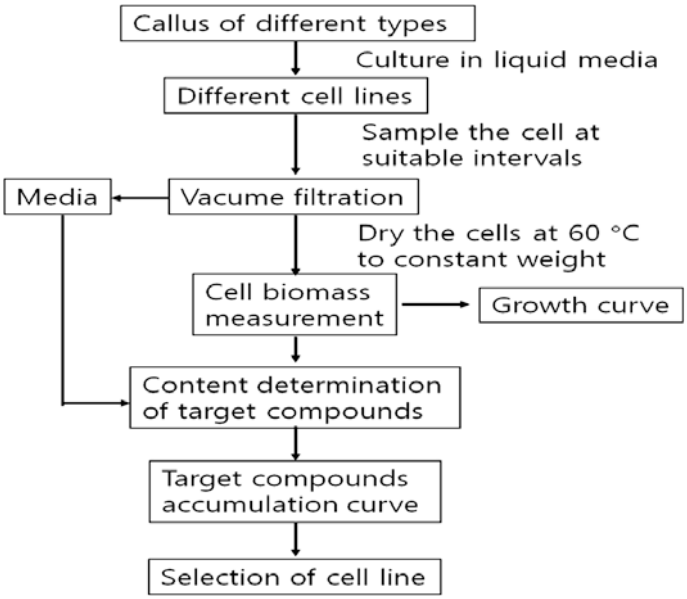

Fig. 9.1 Selection of explant from HYV plant species (cell line)

medium that will be best adapted for cultivation. This medium optimization includes mineral composition and organic constituents with special attention to hormonal balances that govern differentiation mechanisms. This work is now facilitated by the use of incomplete factorial experiments or surface response methods. Once calli are obtained, it is well known that they can undergo soma-clonal variation, usually during several subculture cycles (from several weeks to several years) until genetic stability occurs when each callus can be considered as homogeneous cell aggregate. For stability, growth parameters such as length of lag, of log phases, and growth speed during the log phase may be taken into consideration.

Cell Suspension Cultures

When genetic stability is reached, it is necessary to screen the different callus lines according to their aptitudes to provide an efficient metabolite production (Fig. 9.2). Hence, each callus must be assessed separately for its growth speed as well as intracellular and extracellular metabolite concentrations. This allows an evaluation of the productivity of each cell line (mg of products g^{-1} of cell day^{-1} or mg of products l^{-1} day^{-1}) so that only the best ones will be taken to cell suspensions and reactor studies. Compared to cell growth kinetics, which is usually an exponential curve, most secondary metabolites are produced during the plateau phase. However, some secondary plant products are known to be growth-associated with undifferentiated cells, such as betalains and carotenoids.

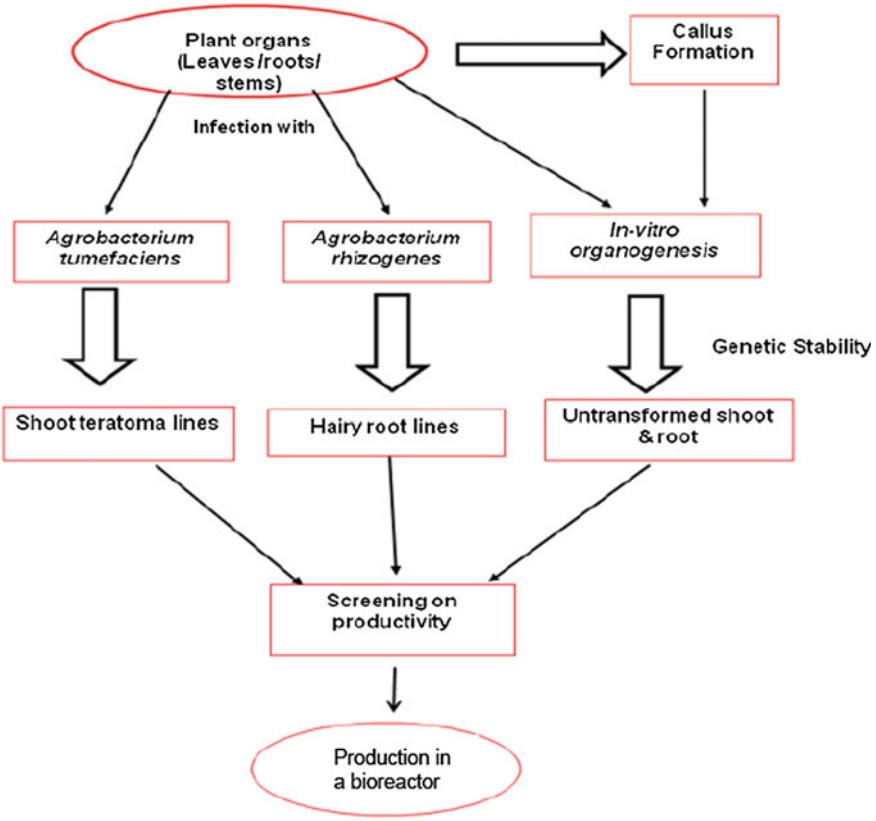

Fig. 9.2 Guidelines for the production of secondary metabolites from plant organ culture

Elicitors

Elicitation by biotic or abiotic elicitors may increase the production of secondary metabolites. It consists in applying by applying stresses by different elicitors to the cell suspension cultures that will trigger the production of secondary metabolites (induction by applied stresses) that are normally not produced. This elicitation can be very efficient at increasing secondary metabolite production as shown in Table 9.3. Addition of biotic and abiotic elicitors like SA and US into the cell suspension culture media of *Taxa baccata* enhanced taxol production independently and when in combination they produced synergic effect (Rezaei et al. 2011).

Bioreactor Cultures

The bioreactors used for culture of plant cells may be of following 4 types: (1) batch bioreactors, (2) continuous bioreactors, (3) multistage bioreactors, and (4) immobilized cell bioreactors; all bioreactors, except the last one, are commonly called stirred tank reactors since the vessel has a device for stirring. Bioreactor studies represent the final step for scaling up the work that leads to commercial production of secondary metabolites from plant cell cultures.

Table 9.3 Effect of salicylic acid (SA) and ultrasound (US) on taxol, a novel anticancer diterpene amide, (mg/l) content of cell suspension culture of *Taxa baccata*

Taxol (mg/l)						
Elicitators		Extracellular	Cell-associated	Total	Release (%)	Specific yield, mg/g cell
SA (mg/l)	US					
0	–	1.54 ± 0.23	2.52 ± 0.65	4.06 ± 0.88	37.93	0.29
	US	5.17 ± 0.89	3.15 ± 0.59	8.32 ± 1.48	62.13	0.62
25	–	10.24 ± 1.56	6.65 ± 1.04	16.89 ± 2.60	60.62	1.60
	US	21.44 ± 3.28	5.34 ± 0.82	26.78 ± 4.10	80.05	2.87
50	–	19.44 ± 2.45	7.54 ± 0.69	26.98 ± 3.14	72.05	3.25
	US	28.76 ± 1.78	4.24 ± 0.43	32.9 ± 2.21	87.11	4.88

SA and US were treated on days 8 and 16 post-inoculation, respectively. Data are mean ± SD, $n = 3$ (*Source* Rezaei et al. 2011)

In batch bioreactors, the medium and inoculum are loaded in the beginning, and the cells are allowed to grow. There is no addition/ replacement of medium, and the entire cell mass is harvested at the end of incubation period. The characteristic features of such bioreactor systems are as follows: (i) continuous depiction of medium, (ii) accumulation of cellular wastes, (iii) alterations in growth rate, and (iv) continuous change in the composition of cells.

In continuous bioreactors, there is continuous inflow of fresh medium and outflow of used medium (with or without cells) during the entire incubation period. A spin-filter bioreactor is a good example of continuous flow, bioreactor; it has the following features: (i) The central shaft of bioreactor houses a spinning filter which enables the removal of used medium, free of cells, through the shaft, (ii) A stirrer plate magnetically coupled to the central shaft provides continuous stirring; the spinning filter also stirs the culture, (iii) The culture is aerated by a sparger which allows a wide range of aeration rates, (iv) A port is provided for addition of fresh medium, while (v) another port enables removal of the culture (used medium + cells) as per need. This bioreactor provides a highly versatile system for control on medium change rate and on cell density; this becomes possible due to the two routes for medium removal while only one of them allows the removal of cells. A continuous flow bioreactor is used to grow cells at a specified cell density in an active growth phase; such cultures may either provide inocula for further culture or may serve as a continuous source of biomass yields.

In case of multistage bioreactors, culture systems use two or more bioreactors in a specified sequence each of which carries out a specific step of the total production process. The simplest situation would involve 2 bioreactors. The commercial production of a biochemical like red pigment shikonin by cultured cells of *Lithospermum erythrorhiza* in Japan is a two-phase process. Both the bioreactors are batch type: the first bioreactor provides conditions for rapid cell proliferation

and favors biomass production in bulk, while the second bioreactor has medium and conditions conducive for shikonin biosynthesis and accumulation.

Immobilized cell bioreactors are based on cells entrapped either in gels, such as, agarose, agar, chitosan, gelatine, gellan, polyacrylamide, and calcium alginate, to produce beads, or in a membrane or metal (stainless steel) screen compartment or cylinder. The membrane/screen cylinder containing cells is kept in a chamber through which the medium is circulated from a recycle chamber. The medium flows parallel to the screen cylinder and diffuses across the screen into the cell mass. Similarly, products from cells diffuse into the medium and out of the screen cylinder. The membrane/screen compartment housing the cells may be cylindrical or flat, and medium movement may so adjust as to flow across the screen compartment rather than parallel to it. The technology is being refined for commercialization. Fresh medium is regularly added, and equivalent volume of used medium is withdrawn from the recycling chamber to maintain its nutrient status.

Cell immobilization changes the physiology of cells as compared to that of cells in suspension. This technique is useful where the biochemical of interest is excreted by the cells into the medium. Product excretion may also be brought about by immobilization itself, or by certain treatments like altered pH, use of DMSO (dimethyl sulfoxide) as a permealizing agent, changed ionic strength of medium, an elicitor. Immobilized cell reactors have the following advantages: (i) no risk of cell wash out, (ii) low contamination risk, (iii) protection of cells from liquid shear, (iv) better control on cell aggregate size, (v) separation of growth phase (in a batch/continuous bioreactor) from production stage (in an immobilized cell bioreactor), and (vi) cellular wastes regularly removed from the system, and (vii) cultures at high cell densities.

Harvest

When secondary products are produced at the end of the growth phase, then two-step reactor is adopted where a first reactor is used for building up the biomass, and a second one for metabolite production. A single-step reactor is sufficient to grow the cells and recover the molecules at the same time when the production of the metabolite is growth-associated. If the metabolites remain intracellular, it is usually necessary to kill the biomass, so that the chemicals can be extracted from the cells following a batch or fed-batch process while extracellular production avoids destruction of the biomass for the extraction of the compounds as they can be directly recovered from the medium following a continuous system with an improved productivity compared to a standard batch. Excretion of intracellular compounds is made possible with permeabilization methods (sonication, pH shock, addition of detergents, oligosaccharides, etc.) without impairing cell viability. Perfusion systems have also been designed with encapsulated cells.

Yield

Some metabolites, especially alkaloids excrete from the cells in the media; therefore, both qualitative and quantitative analyses of secondary metabolites are done on culture media and also on cells. Yields of metabolites are compared on a product

weight per unit weight of cells or on volume of medium basis (Mantell and Smith 1984).

Problems in Large-Scale Plant Cell Culture

Large-scale culture of plant cells for commercial biochemical production presents several problems such as:

(i) Plant cells have much slower growth rates than bacteria and fungi; therefore, larger reactors and longer fermentation times are necessary;
(ii) The long fermentation time increases the risk of contamination;
(iii) Plant cells are rather sensitive to shear, fermenters with conventional mechanical stirring are not suitable for their culture, bioreactors having specially designed mechanical stirrers, or airlift fermenters are far more suitable;
(iv) Plant cells show cytogenetic, genetic, and epigenetic variations during culture, the characteristics of a cell population may change during culture, and prolonged continuous cultures may not be desirable.
(v) In case of biochemical production, often conditions favoring rapid growth may suppress biochemical formation and vice versa, and organized cell masses and cells under stress are more likely to produce useful biochemicals. In all such cases, therefore, a multistage bioreactor system should be employed.

Organ Culture

A wide range of valuable secondary phytochemicals production requires more differentiated micro plant or organ cultures, which becomes essential when the desired metabolite is only produced in specialized plant tissues or glands in the parent plant. Some of the examples are (i) in vitro root culture of ginseng (*Panax ginseng*) is required because saponin and other valuable metabolites are specifically produced in ginseng roots, (ii) hypericins and hyperforins are accumulated only in foliar glands of *Hypericum perforatum* (St. John's-wort) and not in undifferentiated cells, (iii) biosynthesis of lysine to anabasine occurs in tobacco (*N. tabacum*) roots, followed by the conversion of anabasine to nicotine in leaves, and (iv) at least some degree of differentiation in a cell culture must occur before vincristine or vinblastine are synthesized in *Catharanthus roseus*. *Fritillaria unibracteata* can be rapidly propagated, directly from small cuttings of the bulb by the technique of organ culture. The growth rate was about 30–50 times higher than that under natural wild growth conditions, and content of alkaloid and beneficial microelements in the cultured bulbs was higher than found in the wild bulb.

Hairy Root Cultures

Hairy roots (HRs) are obtained after the successful transformation of a plant with *Agrobacterium rhizogenes*. *A. rhizogenes* may be used to transform leaf disks, other organs or even protoplasts. The roots are excised and used to initiate root cultures; usually a culture flask is inoculated with 3–4 roots of 2–3 cm in length. Hairy root cultures are easily developed in most dicot plants. It has received considerable

attention from plant biotechnologists in the two last decades as a method of producing secondary metabolites synthesized in plant roots. The hairy root phenotype is characterized by hormone-independent fast growth, lack of geotropism, profuse lateral roots, and genetic stability. The secondary metabolites produced by HRs are the same as those usually synthesized in intact parent roots, with similar or higher yields. This feature, together with long term genetic stability and generally rapid growth in simple media lacking phytohormones, makes them especially suitable for biochemical studies not easily undertaken with root cultures of an intact plant. A major characteristic of HRs is that they are able to produce secondary metabolites concomitantly with growth. Hence, it is possible to get a continuous source of secondary compounds from actively growing HRs, unlike the usual results obtained with cell suspension cultures. Metabolite production rate may be enhanced by modifying the nutrient composition of the medium or applying elicitors as in case of cell culture.

The hairy roots are normally induced on aseptic, wounded parts of plants by inoculating them with *A. rhizogenes*. The hairy roots (HRs) are differentiated cultures of transformed roots generated by the infection of wounded higher plants with *A. rhizogenes*. This pathogen causes the HR disease leading to the neoplastic growth of roots that are characterized by high growth rate in hormone free media and genetic stability. During the infection process, *A. rhizogenes* transfers a part of the DNA (transfer DNA, T-DNA) located in the root-inducing plasmid Ri to plant cells, and the genes contained in this segment are expressed in the same way as the endogenous genes of the plant cells. Some *A. rhizogenes*, such as strain A4, have the T-DNA divided into two sections: the TR-DNA (right) and TL-DNA (left), each of which can be incorporated separately into the plant genome. Two sets of pRi genes are involved in the root induction process: the *aux* genes located in the TR region of the pRi T-DNA and the *rol* (root loci) genes of the TL region. High stability and productivity features allow the exploitation of HRs as valuable biotechnological tool for the production of plant secondary metabolites. HRs can be also utilized as biological farm for the production of recombinant proteins, hence holding additional potential for industrial use.

Genetic Manipulation in Hairy Root Culture for Secondary Metabolite Production

Transformed roots provide a promising alternative for the biotechnological exploitation of plant cells. *A. rhizogenes*-mediated transformation of plants may be used in a manner analogous to the well-known procedure employing *A. tumefaciens*. *A. rhizogenes*-mediated transformation has also been used to produce transgenic hairy root cultures, and plantlets have been regenerated. None of the other T-DNA sequences are required for the transfer with the exception of the border sequences. The rest of the T-DNA can be replaced with the foreign DNA and introduced into cells from which whole plants can be regenerated. These foreign DNA sequences are stably inherited in a Mendelian manner. The *A. rhizogenes*-mediated transformation has the advantage of being able to transfer any foreign gene of interest placed in binary vector to the transformed hairy root clone,

e.g., the 6-hydroxylase gene of *Hyoscyamus muticus* introduced to hyocyamin-rich *A. belladonna* by a binary vector system. Engineered roots showed an increased amount of enzyme activity and a fivefold higher concentration of scopolamine.

Shoot Cultures

As with roots, it is possible to cultivate plant aerial parts (shoots) for the production of secondary metabolites (Fig. 9.2). Shoot cultures can be transgenic, the so-called shooty teratomas, if they are obtained after infection with *Agrobacterium tumefaciens*, or non-transgenic through the simple use of appropriate hormonal balance. Shoots exhibit genetic stability, good capacities for secondary metabolite production, and a link between growth and the production of secondary compounds, some of the comparable properties to hairy roots.

Organ Cultures in Bioreactors

Compared to cell suspension cultures, organ cultures generally display a lower sensitivity to shear stress with some exceptions. *Catharanthus roseus* hairy roots need to be cultivated in an air-sparged bioreactor. Immobilization of hairy roots into a polymer matrix is a well-known technique, and it is also possible to protect the roots from agitation by using screens or wire meshes. Other less sensitive organs can be cultivated in stirred bioreactors. One of the major problems encountered with organ cultures in bioreactors is due to the inhomogeneous character of the biomass compared to thin cell suspensions. Hairy roots in liquid systems grow in approximately spherical clumps but display a high degree of spatial heterogeneity. This heterogeneity can be partially attributed to inhomogeneous and limiting mass transfers to the roots, regarding oxygen and nutrients.

Due to their genetic stability, organs are less submitted to erratic metabolite production than undifferentiated cells except a spatial heterogeneity along the growing organ. The total root biomass is always composed of young (root tip) and older tissues, and these young and old tissues present various possibilities for the synthesis of secondary compounds. Young tips of *Psoralea* roots were more capable of synthesizing isoflavones (daidzein), whereas old roots accumulated isoflavone-derivatives like coumestrol.

In most organ cultures, the production of secondary plant products is usually concomitant with growth. As a consequence, it is possible to use a single-stage bioreactor for both growing the biomass and producing the compounds; most of the secondary metabolites tend to remain intracellular, especially when growth is still active.

Specific bioreactors have been designed for hairy root cultures in order to overcome the limiting factors existing for biomass and secondary metabolite production. Submerged cultures have successfully been replaced by dispersed liquid systems such as nutrient mist reactors or drip-tube techniques. Two-phase systems have also been used to facilitate the release and recovery of the secondary compounds in the medium. This technology helps to continuously remove the compounds from the medium and helps to prevent the feedback repression of the synthesis. Despite all the improvements that have been made to reach a better understanding of plant organ cultures in bioreactors, this technology has led to even

fewer commercial successes than cell suspension cultures for the production of secondary metabolites.

9.2.3 Industrial Application

9.2.3.1 Commercial Production of Shikonin

Shikonin (dye) was the first commercial product from cell cultures. This became possible due to the following:

Development of media for (i) biomass production, (ii) biochemical production, (iii) isolation of stable high-producing cell clones, and (iv) use of a two-stage production system. The high-producing clone cells to be used as inoculum. The inoculum is first added to a 200-l fermenter (first stage) containing the MG-5 medium for culture growth. After 9 days, the cells are filtered out and inoculated into a 750-l fermenter (second stage) containing M-9 shikonin production medium and incubated for 14 days. The cells are harvested by simple filtration, and shikonin and shikonin derivatives are extracted from the cells.

A 750-l bioreactor with 600 l medium would yield 1.2 kg of shikonin in 2 weeks. In contrast, Lithospermum roots from 1 ha land would yield about 9 kg shikonin after 4 years. Thus, 8 runs of 2 weeks of the bioreactor become equivalent to 4 years of a 1 ha field of *Lithospermum erythrorhizon* in terms of shikonin yields. Cell-culture-derived shikonin has been used in Japan since 1984 in the manufacture of cosmetics, lotion, and soap.

9.2.3.2 Biotransformation of Drug Precursors

Plant cells have the potential to produce, either by de novo synthesis or by biotransformation of specific precursors, an extensive range of secondary metabolites in culture. Modification of an exogenous compound by plant cells (or other biological entities) is called biotransformation or by conversion. The bioconversion reactions are catalyzed by enzymes present in plant cells. These reactions include esterification, oxidation, reduction, hydroxylation, and glycosylation. In all cases, the stereo—and regioselectivity expressed by the in vivo process is of enormous advantage. However, the low rates of biotransformation have prevented commercial exploitation of the very large number of bioconversions known for plant cells. The interest in bioconversion is mainly because the product of the process is more useful or valuable than the precursor used.

A relatively high rate of bioconversion (0.8 g/1 medium over 7-day period) of cardiac glycosides is affected by *Digitalis lantana* cell cultures. Digitalis cells hydroxylate the C-12 position of *p*-methyldigitoxin to convert it into *p*-methyldigoxin, which is more valuable than the former. Cell cultures of several species, i.e., *Datura innoxia*, *Catharanthus roseus*, *Rauwolfia serpentina*, biotransform

hydroquinone into its β-D-glucoside called arbutin. Arbutin is an efficient suppressor of melanin biosynthesis in human skin and is used in cosmetics. Catharanthus cells biotransform hydroquinone into arbutin at the rate of 9.2 g/1 of medium over 4 days, while Rauwolfia cultures give arbutin yield of 18 g/1 medium in 7 days. Arbutin is at present prepared chemically in a 3-step procedure. But it is expected that refinements may enable the single-step biotransformation process to outcompete the chemical procedure.

There is a wide scope for the industrial application of secondary metabolites from plant sources as indicated in Table 9.4.

Most of the above and many other secondary metabolites may be derived from plant cell/organ culture in vitro. However, these cultures exhibit relatively slow rates of growth, and the biosynthesis of the desired compounds is often at a much lower level than in the intact plant. In order for cell cultures to be used as commercial sources of these compounds, the in vitro production must be comparable to or to exceed the amount produced by the intact plant (Table 9.2).

Vanisree et al. (2004) noted the recent advances in tissue culture technology for the production of a wide variety of plant pharmaceuticals like alkaloids, terpenoids, steroids, saponins, phenolics, flavonoids, and amino acids, especially taxol, morphine and codeine, ginsenosides, L-DOPA, berberine, diosgenin, capsaicin, camptothecin, vinblastine and vincristine, tanshinones, Podophyllotoxin. In tissue culture technology, transcription factors are considered efficient new molecular tools for plant metabolic engineering to increase the production of valuable compounds (Gantet and Memelink 2002). The anticancer agent paclitaxel yield is low in nature, and plant cell culture technology is an amenable attractive alternative to scale-up production (Kolewe et al. 2008). Several published reports also indicated the in vitro culture yields exceeded that of the whole plant. Undoubtedly, the

Table 9.4 Secondary metabolites from plants and their associated industries

Industry	Plant product	Plant species	Industrial uses
(a) Pharmaceuticals	Codeine (alkaloid)	*Papaver somniferum*	Analgesic
	Diosgenin (steroid)	*Dioscorea deltoidea*	Antifertility agents
	Quinine (alkaloid)	*Cinchona ledgeriana*	Antimalarial
	Digoxin (cardiac glycoside)	*Digitalis lanata*	Cardiotonic
	Scopolamine (alkaloid)	*Datura stramonium*	Antihypertensive
	Vincristine (alkaloid)	*Catharanthus roseus*	Antileukemic
(b) Agrochemicals	Pyrethrin	*Chrysanthemum cinerariaefolium*	Insecticide
(c) Food and drink	Quinine (alkaloid)	*Cinchona ledgeriana*	Bittering agent
	Thaumatin (chalcone)	*Thaumatococcus danielli*	Non-nutritive sweetener
(d) Cosmetics	Jasmine	*Jasminum* sp.	Perfume

biosynthesis of compounds in vitro has many possibilities, although a number of the problems associated with it still need extensive research before this new technique can be applied on a large scale.

9.2.4 Animal Tissue Culture

Animal tissue culture generally involves the removal of cells tissues, or organs from an animal and their subsequent placement into an artificial environment (in vitro culture medium) conducive to growth.

Animal Cell Cultures
The in vitro cultivation of cell tissue and organ of animal origin is collectively known as animal tissue culture and is now used in many areas of science. The partial list of different cell types which can be grown in culture includes connective elements such as fibroblasts, skeletal tissue (bone and cartilage), skeletal, cardiac and smooth muscle, epithelial tissue (liver, lung, breast, skin, bladder, and kidney), neural cells (glial cells and neurons, although neurons do not proliferate in vitro), endocrine cells (adrenal, pituitary, pancreatic islet cells), melanocytes, and many different types of tumor cells. Tissue culture can be subdivided into three major categories such as cell culture, explant culture, and organ culture.

Cell Culture
Cell culture refers to cultures derived from dissociated cells taken from the original tissue ('primary cell culture'). Cells are dispersed (mechanically and/or enzymatically) into a cell suspension which may then be cultured as a monolayer on a solid substrate, or as a suspension in the culture medium.

Explant (or Organotypic) Culture
In explant culture, small pieces of the tissue of interest are simply allowed to attach to an appropriate substrate, usually one that has been coated with collagen, and are cultured in a rich medium, usually one containing serum.

Organ Culture
Organ culture refers to a three-dimensional culture of tissue retaining some or all of the histological features of the tissue in vivo. The whole organ or part of the organ is maintained in a way that allows differentiation and preservation of architecture.

Basic Equipment and Facilities Requirement in Animal Cell Culture
Some of the specific equipment and techniques are required for the maintenance of cell cultures. A rule of thumb is that the more equipments are available, the more efficient cell culturing be performed.

Sterile Work Area
A separate clean room equipped with an airflow cabinet, e.g., HEPA (High Efficiency Particle Air Filter) for filtered air supply around the work surface should be made available for clean cell culture work. A laminar flow hood offers the best

sterile protection available. All work surfaces, benches and shelves, and the base of the airflow cabinets must be kept clean by frequent swabbing with 70% ethanol or an alternative disinfectant.

Incubation Facilities

In addition to an airflow cabinet and benching which can be easily cleaned, the cell culture laboratory will need to be furnished with an incubator or hot room to maintain the cells at 30–40 °C. The incubation temperature will depend on the type of cells being cultivated. It may be necessary to use an incubator which has been designed to allow CO_2 to be supplied from a main supply or gas cylinder so that an atmosphere of between 2 and 5% CO_2 is maintained in the incubator. In general, many cell lines can be maintained in an atmosphere of 5% CO_2:95% air and at 99% relative humidity.

Refrigerators and Freezer (−20 °C)

Both items are very important for storage of liquid media at 4 °C and for enzymes (e.g., trypsin) and some media components (e.g., glutamine and serum) at −20 °C. A refrigerator or cold room is required to store medium and buffers. A freezer will be needed for keeping pre-aliquoted stocks of serum, nutrients, and antibiotics. Reagents may be stored at a temperature of −20 °C but if cells are to be preserved it may be necessary to provide liquid nitrogen or a −70 °C freezer.

Microscopes

A simple inverted microscope is essential so that cultures can be examined in flasks and dishes. It is vital to be able to recognize morphological changes in cultures since these may be the first indication of deterioration of a culture. A very simple light microscope with 100× magnification will suffice for routine cell counts in a hemocytometer. A camera, CCD video camera, adapter and attachments, and UV facility may also be required for some purposes.

Tissue culture ware

A variety of tissue culture plasticware is available (specially treated polystyrene). Cells can be maintained in petri dishes or flasks (25 or 75 cm^2) which have the added advantage that the flasks can be gassed and then sealed so that a CO_2 incubator need not be used.

Washing Up and Sterilizing Facilities

Glassware such as pipettes should be soaked in a suitable detergent and then passed through a stringent washing procedure with thorough soaking in distilled water prior to drying and sterilizing. Glassware, such as pipettes, conical flasks, beakers (covered with aluminum foil), are sterilized in a hot air oven at 160 °C for 1 h. All other equipment, such as automatic pipette tips and bottles (lids loosely attached), are autoclaved at 121 °C for 20 min. Sterilizing indicators such as sterile test strip are necessary for each sterilizing batch to ensure that the machine is operating effectively. Autoclave bags are available for loose items. Aluminum foil also makes good packaging material.

Liquid N_2/Deep Freezer

Invariably for continuous and finite cell lines, samples of cultures will need to be frozen down for storage. It is important to maintain continuity in cells to prevent genetic drift and to guard against loss of the cell line through contamination and other disasters. The procedure for freezing cells is general for all cells in culture. They should be frozen in exponential phase of growth with a suitable preservative, usually dimethylsulfoxide (DMSO). The cells are frozen slowly at 1 °C/min to −50 °C and then kept either at −196 °C immersed in liquid N_2 (in sealed glass ampoules) or above the liquid surface in the gas phase (screw top ampoules). Deterioration of frozen cells has been observed at −70 °C, therefore, −196 °C (liquid N_2) seems to be necessary.

Water Still or Reverse Osmosis Apparatus

A double-distilled (glass distilled) or reverse osmosis water supply is essential for preparation of media, and rinsing glassware. The pH of the double-distilled water should be regularly checked.

Water is sterilized by autoclaving at 121 °C for 20 min. The distilled water must be stored in glass if it is to be used for the preparation of media.

Filter Sterilization

Media that cannot be autoclaved must be sterilized through a 0.22-μm-pore-size membrane filter. These are obtainable in various designs to allow a wide range of volumes to be filtered (e.g., Millipore, Gelman).

Facilities for Counting Cells

It is possible to monitor cell growth by eyes (looking for confluency). More accurate cell counts are required for most experimental purposes, and the most commonly used device is the improved Neubauer hemocytometer originally designed for counting blood cells.

General Small Items of Equipment

A number of small items of equipment are useful for performing cell culture, e.g., water bath and centrifuge with sealed buckets, vacuum pump, graduated pipettes of various sizes, centrifuge tubes and universal containers, disposable Pasteur pipettes, rubber bulbs for use with Pasteur pipettes, glass or plastic pipettes for large volume, precisely calibrated automatic pipettes (small volumes of 1–1000 μl) with disposable, autoclavable, plastic tips, suction aid such as ‘Pipet-aid’ or ‘pi-pump’, etc., are necessary.

Culture Media

The tissue culture media essentially consists of metabolites (e.g., carbohydrates, amino acids, vitamins, proteins, and peptides), inorganic ions, hormones and extracellular matrix, and also the biological fluid for culturing cells, serum. The environment is regulated with regard to the temperature, osmotic pressure, pH, etc., which closely simulate the situation in vivo.

A wide variety of culture media is currently available. The choice of culture media is dependent on the requirements of cells. The components of suitable culture media include:

Basic Media
The most basic media are balanced salt solutions (BSS), e.g., phosphate-buffered saline (PBS), which may be used for washing cells and for short incubations in suspension. More complex defined media are used for growth and maintenance. Defined media can also vary in complexity, by the addition of a number of constituents, e.g., from Eagle's minimum essential medium (MEM) which contains essential amino acids, vitamins, and salts, to McCoy's medium, which contains a larger number of different amino acids, vitamins, minerals, and other extra metabolites (such as nucleosides).

Buffering Capacity
Cell cultures have an optimum pH for growth, generally between pH 7.4 and 7.7. The type of buffering that is used for the media depends on the growth conditions. When cells are incubated in a CO_2 atmosphere, an equilibrium is maintained between the medium and the gas phase. A bicarbonate–CO_2 buffering system is most often used due to its low toxicity toward the cells.

Glutamine and Amino Acids
In addition to buffering the medium, there are other growth requirements including amino acids, the requirement for which may vary with cell culture type. Commonly the necessary amino acids include cysteine and tyrosine, but some non-essential amino acids may be needed. Glutamine is also required by most cell lines, and it has been suggested that cultured cells use glutamine as an energy and carbon source in preference to glucose, although glucose is present in most defined media. Glutamine is usually added at a final concentration of 2 mM; however, once added to the medium, the glutamine is only stable for about 3 weeks at 4 °C.

Serum
Various sources of serum may be used such as calf, fetal calf, and horse. Many continuous cultures utilize calf serum, but often fetal calf serum provides the best growing conditions. The level of serum used depends on the particular cell line and should be determined empirically.

Antibiotics and Antimycotics
In absence of good sterile conditions, it is necessary to incorporate antibiotics and antimycotics into the media like penicillin/streptomycin solutions, or broader spectrum antibacterial/antimycotic agents such as kanamycin or amphotericin B. The antibiotics chosen should clearly not to be toxic to the cells in culture.

Supply and Preparation of Culture Media
The choice of culture media used will depend on the type of primary cell, cell line, and the incubation conditions. However, it is best to start with the medium recommended by the original supplier of the cells.

Culturing Animal Cells
Selecting Sources of Tissue for Culture

Adult or embryonic tissue
Cultures can be derived from adult tissue or from embryonic tissue. Cultures derived from embryonic tissue generally survive and grow better than those taken from adult tissue. Tissues from almost all parts of the embryo are easy to culture, whereas tissues from adult are often difficult or even impossible to culture.

9.2.5 Animal Products in Therapeutic Use

The WHO estimates that as many as 80% of the world's more than six billion people rely primarily on animal- and plant-based medicines. Ingredients sourced from wild plants and animals are used in traditional medicines and as raw materials also in the preparation of modern medicines and herbal preparations (Kang and Phipps 2003).

Animals and products derived from different organs of their bodies have constituted part of medicinal substances in different cultures since ancient times (Adeola 1992; Agrimi et al. 1992; Lev 2003); such uses still exist in traditional medicine. The healing of human ailments by using therapeutics based on medicines obtained from animals is known as zootherapy (Costa-Neto 2005) In modern societies, zootherapy constitutes an important alternative therapy and wild and domestic animals, and their by-products (e.g., hooves, skins, bones, feathers, tusks) form important ingredients in the preparation of curative, protective, and preventive medicine (Adeola 1992, Agrimie et al. 1992). Traditional Chinese Medicine (TCM) contains more than 1500 animal species (Anonymous 1995); in India, nearly 15–20% of the Ayurvedic medicine is based on animal-derived substances (Unnikrishnan 1998) and in Bahia State, in the northeast of Brazil, over 180 medicinal animals have been recorded (Neto 2004).

Animal metabolites of therapeutic application include a wide-spectrum product such as: Carmine (red dye) is made from crushed female cochineal insects. It is also known as natural red 4. Gelatin is a protein that is obtained by boiling the skin, ligaments, tendons, and bones from cows and pigs in water. The capsule cover of modern drug is made from gelatin. Glycerin may be obtained from cow or pig fat. Heparin anticoagulant medication is derived from cows (lungs) and pigs (intestines). Insulin—much of the insulin on the market is made from hog pancreas, diabetics can also get synthetic insulin. Lactose is extremely common and is milk sugar from mammal milk. Lanolin is a product of the oil glands of sheep. It is an ingredient in some ophthalmic drugs (found in eye drops because it has antibacterial properties) and is used as a carrier in certain drugs that are given by injection. Magnesium stearate—the stearate portion of magnesium stearate is a form of stearic acid, which is a saturated fat, found in cows, coconut oil, cocoa butter, and other foods and depending on the origin, it may be of animal or plant product. Premarin is

a conjugated estrogen product comes from horse urine. Vaccines for both children and adults, including the flu vaccine, contain animal by-products or are prepared with them, including gelatin, chicken embryo, guinea pig embryo cells, and serums. If some of the animal-derived products are synthesized by biotechnological methods, then the pressure on animals would be minimized proportionately. At present, about 40% of all prescription drugs are substances originally extracted from plants, animals, fungi, and microorganisms (Wilson 1995). The use of animals in popular medicine certainly provokes pressure on natural resources exploited through traditional forms of collection, mainly due to general acceptance of popular medicine (Almeida and Albuquerque 2002). The world is facing potentially massive loss of wildlife due to over-hunting (Robinson and Bennett 2000; Bennett et al. 2002).

Nowadays, animal cell culture becomes a reasonable alternative for animal experiments in the process of drug discovery and development. Overall, an aspect of pharmaceutical research which promisingly employs cell culture models is the study of in vitro drug transport/absorption and metabolism. More recently, cultured animal cells have been preferred for the expression of human genes encoding pharmaceutically valuable proteins. Some of these proteins have already been approved for therapeutic use, e.g., hGH (for dwarfism), tissue plasminogen activator (tPA; thrombolysis) crythropoietin (anemia), and blood clotting factor VIII (hemophilia); the last two of the proteins have been approved for marketing in India.

9.2.6 Fermentation and Production of Microbial Primary and Secondary Metabolites

Any of a group of chemical reactions induced by microorganisms or enzymes (ferments) that split complex organic compounds like sugar into relatively simple substances such as acetic acid, citric acid, ethanol, CO_2, and energy. Industrial fermentation is the intentional use of fermentation by microorganisms such as bacteria and fungi are used intentionally in industrial fermentation to make useful products. Fermented products have applications as food as well as in general industry. Some commodity chemicals are made by fermentation.

Fermentations (or industrial fermentations) based on the end-product application can be divided into four types (Stanbury et al. 1999):

(a) Biomass production—the end product is viable cellular material single cell protein, baker's yeast, probiotic cultures;
(b) Production of extracellular metabolites—Chemical compound intermediates of microbial biochemical pathways are produced and can be divided into two groups:

(i) Primary metabolites (produced during the growth phase of the organism, e.g., ethanol, citric acid, glutamic acid, lysine, vitamins, and polysaccharides)
(ii) Secondary metabolites (produced during the stationary phase, e.g., penicillin, cyclosporin A, gibberellin, and lovastatin);

(c) Production of intracellular components—enzymes and other proteins production, followed cell lysis at the end and purification of the products; and
(d) Transformation of substrate—raw material is biologically transformed into a finished product and generally used for steroid transformations, food fermentations, and sewage treatment.

Single cell protein, bakers yeast, lactobacillus, *E. coli*, etc., are the intended microbial cells or biomass products of fermentation.

Microbial metabolites are divided into two broad groups: (i) primary metabolites produced during the growth phase of the organism (e.g., ethanol, citric acid, glutamic acid, lysine, vitamins, and polysaccharides) and (ii) secondary metabolites produced during the stationary phase (e.g., penicillin, cyclosporin A, gibberellin, and lovastatin).

Intracellular components of microbial origin include microbial enzymes (catalase, amylase, protease, pectinase, glucose isomerase, cellulase, hemicellulase, lipase, lactase, streptokinase) and many others and recombinant proteins (insulin, hepatitis B vaccine, interferon, granulocyte colony-stimulating factor), etc. The cells are ruptured (lysed) at the end of fermentation to release the products.

Substrate transformation involves the transformation of a specific compound into another, such as in the case of phenylacetylcarbinol, and steroid biotransformation, or the transformation of a raw material into a finished product, in the case of food fermentations and sewage treatment. Ancient fermented food processes, such as making bread, wine, cheese, curds, idli, dosa, etc., also constitute biotechnology. Marmite (made from yeast extract) is a by-product of beer brewing. Other products similar to marmite are: Australian Vegemite, Swiss Cenovis, and German Vitam-R.

In the process of sewage treatment, sewage is digested by enzymes secreted by bacteria into harmless, soluble substances, carbon dioxide, methane, etc. Digested solids is dried and used as fertilizer and gaseous by-products (methane) can be utilized as biogas. Liquids that result are disinfected before being discharged into rivers or the sea or can be used as liquid fertilizers.

Bacterial metabolism can be classified into three major categories viz. (i) the kind of energy used for growth, (ii) the carbon source, and (iii) the electron donors used for growth. Metabolites, the metabolic intermediates and products, are typically characterized by small molecules with various functions. Metabolites can be categorized into (i) primary and (ii) secondary metabolites. These metabolites can be used in industrial microbiology to get various types of chemicals such as amino acids, vaccines, antibiotics, and other chemicals necessary for organic synthesis. They are produced in two different phases of the life cycle of the organism (Fig. 9.3).

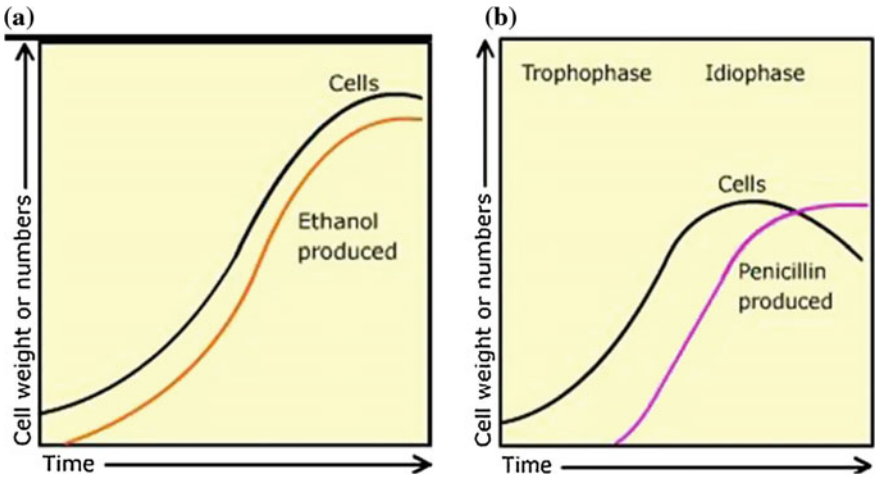

Fig. 9.3 **a** A primary metabolite ethanol from yeast has a production curve that lags only slightly behind the line showing cell growth. **b** Secondary metabolite penicillin from mold begins to be produced only after the logarithmic growth phase of the cell (trophophase) is completed. The main production of the secondary metabolite occurs during the stationary phase of cell growth (idiophase)

9.2.6.1 Primary Metabolites

Primary metabolites of microorganisms are involved in growth, development, and reproduction of the organism. The primary metabolite, often referred to as a central metabolite, is typically a key component in maintaining normal physiological processes of the organism. They are essential for proper growth, and they are typically synthesized during the growth phase as a result of energy metabolism and include alcohols (ethanol), lactic acid, citric acid, amino acids (glutamic acid, lysine), vitamins, polysaccharides. In industrial microbiology, alcohol fermentation by *Saccharum officinarum* fungus is most common primary metabolite product used for large-scale production of beer and wine, citric acid is produced by *Aspergillus niger*, glutamate, lysine, threonine, tryptophan, and other amino acids are produced by some *Micrococcus* sp. and *Corynebacterium* sp. (e.g., *Corynebacteria glutamicum*). These products are most widely used ingredients in food, pharmaceutical and cosmetic industries.

9.2.6.2 Secondary Metabolites

Secondary metabolites are produced through the modification of primary metabolites, and they do not play a role in growth, development, and reproduction or other vital processes of the organisms but in defense and in similar ecological functions. The secondary metabolites are produced during the stationary phase of cell growth

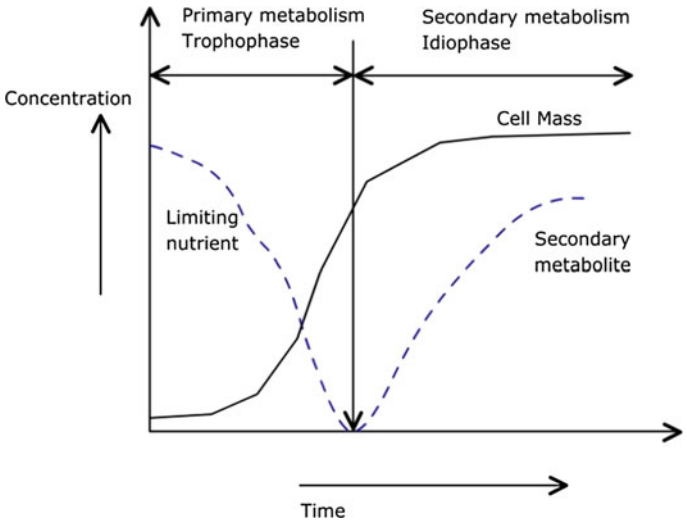

Fig. 9.4 Primary and secondary metabolism. During the trophophase, the cell mass increases logarithmically but as the resources become limiting, growth rate drops and production stops. Idiolites are special metabolites usually possessing bizarre chemical structures, and although not essential for the producing organism's growth in pure culture, they have survival functions in nature

(idiophase). Penicillin, cyclosporin A, erythromycin, lovastatin, bacitracin, etc., are good examples of secondary metabolites. Penicillin is synthesized by *Penicillium* molds that prevents bacterial growth, bacteria *Bacillus subtilis,* and other *Lactobacillus* sp. are able to produce bacteriocins (non-ribosomal peptides) which prevent the growth of bacteria either as antibiotics or as antiseptics (gramicidin S) is commonly used a topical drug. Erythromycin, derived from *Saccharopolyspora erythraea*, is a commonly used antibiotic with a wide antimicrobial spectrum. Griseofulvin fungicides are also produced as secondary metabolites. Typically, secondary metabolites are not produced in the presence of glucose or other carbon sources which would encourage growth, and like primary metabolites are released into the surrounding medium without rupture of the cell membrane (Fig. 9.4).

9.3 Some High-Value Medicinal Plants Including Spices, Beverage, Aromatic Plants

High-value medicinal plants

There are hundreds of herbs, and their parts (leaf, flower, fruit, root, rhizome, etc.) serve all kinds of important medicinal and health purposes ranging from anti-inflammatory, antifungal, insect repellent, antiseptic, remedies for injuries, scrapes and bites, expectorant, antibacterial, detoxification, fever reduction,

antihistamine to pain relief. They grow in nature, some are cultivated and some are available in local market for purchase. These plants are valuable for medicinal use, culinary purposes, and also valuable because they provide a means of earning the livelihood of a group of rural people. They are also valuable in different traditional systems of indigenous medicines and source of lead compounds and drug principles of modern medicine. Hundreds of medicinal plants (including spices, culinary, and aromatic herbs) are traded worldwide, and many of them are considered to be of very high-value items per weight among the traded plants and plant products. These pharmaceutical cash crops have a huge potential for rural communities that practice subsistence agriculture with insignificant access to main stream economy (Dubey et al. 2004; Chauhan et al. 2013; Sher et al. 2014). These minor crops have relatively small contribution to total agricultural output of a country, but their value in global trade is significant; it was about US$60 billion in 2006 (Adhikari 2001; Hamilton 2006). Collection, cultivation, and trade (internal and world trade) of medicinal plants in many Asian countries constitute an age-old practice (Ali-Shtayeh et al. 2000; Lev and Amar 2002; Ghorbani 2005; Al-Quran 2008). Europe imports about US$ 1 billion in MAPs from Africa and Asia annually (Ghimire et al. 2002; Sher and Hussain 2009), and it is expected to expand substantially by the year 2050 because of the increasing trend in herbal medicine use (Lange 1999; Al-Quran 2008; Khan et al. 2011).

High-value medicinal plants may be from cultivated crops, forest grown, or wild source plants. Some of the examples of high-value medicinal plants include *A. moschatus*, *Abies spectabilis*, *Abrus precatorius*, *Achyranthes aspera*, *Aconitum ferox*, *A. heterophyllum*, *Acorus calamus*, *Acacia catechu*, *A. sinuate*, *A. marmelos*, *Aesculus hippocastanum*, *Adhatoda zeylanica*, *Adiantum capillus-veneris*, *Albizzia amara*, *Aloe barbedensis*, *A. vera*, *Alpinia calcarata*, *Alstonia scholaris*, *A. paniculata*, *Angelica sinensis*, *Anogeissus latifolia*, *A. annua* and other *Artemisia* sp., *Asparagus adscendens*, *A. racemosus*, *Astragalus membranaceus*, *Aerva lanata*, *A. indica*, *B. monnieri*, *Baliospermum montanum*, *B. aristata*, *B. vulgaris*, *B. erythroclada*, *Bergenia ciliate*, *Boerhavia diffusa*, *Boswellia serrata*, *Bunium persicum*, *Butea monosperma*, *Caesalpinia sappan*, *Cardiospermum halicacabum*, *Cassia absus*, *C. angustifolia*, *C*, *fistula*, *C. tora*, *Catharanthus roseus*, *Cedrus deodara*, *C. paniculatus Centella asiatica*, *Centratherum anthelminticum*, *Cephaelis peruviana*, *Citrullus colocynthis*, *Careya arborea*, *Chlorophytum borivillanum*, *C. tuberosum*, *Cinnamomum sulphuratum*, *C. tamala*, *Cichorium intybus*, *Chlorophytum borivilianum*, *Chrysopogon zizanioides*, *Clerodendrum phlomides*, *Colchicum luteum*, *Commiphora caudate*, *C. mukul*, *C. wightii*, *Convolvulus pluricaulis*, *Coptis chinensis*, *Coscinium fenestratum*, *Crataegus* spp., *Croton tiglium*, *Curculigo orchioides*, *Curcuma angustifolia*, *C. zerumbet*, *Cymbopogon cytratus*, *Cyperus esculentus*, *C. rotundus*, *Cyclea peltata*, *Datura metel*, *Decalepis hamiltonii*, *Desmodium gangeticum*, *D. deltoidea*, *Diospyros lotus*, *Echinacea* spp., *Eclipta prostrate*, *E. prostate*, *Eleutherococcus senticosus*, *E. officinalis*, *Embelia ribes*, *E. tsjerium-cottam*, *Ephedra gerardiana*, *Ficus benghalensis*, *Ficus religiosa*, *Fumaria indica*, *Garcinia indica*, *G. glabra*, *G. sylvestre*, *Gardenia resinifera*, *Geranium wallichianum*, *Gingko biloba*, *Gloriosa superba*,

Gmelina arborea, *G. sylvestre*, *Gynura procambens*, *Hedyotis corymbosa*, *Helicteres isora*, *Hemidesmus indicus*, *Holarrhena pubescens*, *Holoptelea integrifolia*, *Holostemma ada-kodien*, *Hydnocarpus kurzii*, *Hydrastis canadensis*, *Hypericum perforatum*, *Hygrophylla schulli*, *Indigofera tinctoria*, *Inula racemosa*, *Ipomoea mauritiana*, *Ipomoea nil*, *Ixora coccinea*, *Jatropha curcas*, *Juniperus communis*, *Jurinea himalaica*, *J. macrocephala*, *Kaempferia galangal*, *Lannea coromandelica*, *Lawsonia inermis*, *Lepidium sativum*, *Litsea glutinosa*, *Lobelia nicotianaefolia*, *Madhuca indica*, *Mecanopsis grandis*, *M. peniculata*, *Mentha arvensis*, *Merremia tridentate*, *Messua ferrea*, *Mimusops elengi*, *Morchella esculenta*, *Morinda pubescens*, *Mucuna puriens*, *Nardostachys grandiflora*, *N. jatamansi*, *Neopicrorhiza scrophulariiflora*, *Nilgirianthus ciliates*, *Ocimum americanum*, *O. basilicum*, *O. sanctum*, *O. tenuiflorum*, *Onosma hispidum*, *Operculina turpethum*, *Oroxylum indicum*, *Paeonia emodi*, *Panax ginseng*, *P. somniferum*, *Paris polyphylla*, *Parmelia perlata*, *Peganum harmala*, *Persicaria amplexicaulis*, *Phyllanthus amarus*, *Picrorhiza kurroa*, *P. longum*, *P. nigrum*, *Picrohiza kurroa*, *Pistacia chinensis*, *P. integerrima*, *Plantago ovata*, *P. psyllium*, *Pluchea lanceolata*, *Plumbago zeylanica*, *Plantago ovate*, *Plectranthus barbatus*, *P. peltatum*, *Pogostemon cablin*, *Pongamiapinnata*, *Polygonatum multiflorum*, *Potentilla peduncularis*, *Prunus armeniaca*, *Pseudarthia viscida Psoralea corylifolia*, *Premna serratifolia*, *Pterocarpus marsupium*, *P. santalinus*, *R. serpentina*, *Rhamnus purshianus*, *Rheum austral*, *Rhododendron anthopogon*, *Rubia cordifolia*, *S. album*, *Sapindus mukorossi*, *Saraca asoca*, *Saussurea costus*, *S. lappa*, *Serenoa repens*, *Silybum marianum*, *Simmondsi chinensis*, *Schrebera swietenioides*, *Semecarpus anacardium*, *Sida rhombifolia*, *Sinopodophyllum hexandrum*, *Sisymbrium irio*, *Solanum anguivi*, *S. nigrum*, *S. virginianum*, *Smilax glabra*, *Soymida febrifuga*, *Sphaeranthus indicus*, *Sterculia urens*, *Stereospermum chelonoides*, *Strychnos nux-vomica*, *S. potatorum*, *Symplocos racemosus*, *Swertia chirayita*, *T. wallichiana*, *Tephrosia purpurea*, *Terminalia arjuna T. bellirica*, *T. chebula*, *T. cordifolia*, *Trachyspermum ammi*, *Tragia involucrate*, *Tribulus terrestris*, *Trichosanthes cucumerina*, *Trillium govanianum*, *Urtica dioca*, *Uncaria* sp., *Valeriana jatamansii*, *Vateria indica*, *Viola pilosa*, *Vetiveria zizanioides*, *Vitex negundo*, *Withania coagulens*, *W. somnifera*, *Woodfordia fruticosa Wrightia tinctoria*, *Zanthoxylum nepalense*, *Ziziphus jujube*, *Z. xylocarpus*, etc. (Gupta and Chadha 1995; Ayensu 1996; Grünwald and Büttel 1996; Laird 1999).

9.4 Trade of Herbal Drugs

Medicinal and Aromatic Plants in Trade

Medicinal and aromatic plants have been offering in a wide variety of products on the market. At least every fourth flowering plant is used for the purpose. The enormous demand in botanicals results in a huge trade from local to international level. In the 1990s, the reported annual worldwide importation of pharmaceutical

Table 9.5 The world's top 12 leading countries of import and export of pharmaceutical plants, according to average quantities and values for the period 1991–2000

Country of import	Quantity (t)	Value (USD)	Country of export	Quantity (t)	Value (USD)
Hong Kong	67,000	291,200,000	China	147,000	281,800,000
Japan	51,350	136,000,000	Hong Kong	63,150	228,800,000
USA	49,600	135,500,000	India	33,900	56,650,000
Germany	45,350	110,200,000	Germany	15,100	70,050,000
Rep. Korea	32,250	52,300,000	USA	13,500	115,500,000
France	21,350	52,000,000	Mexico	13,000	11,250,000
China	13,650	41,600,000	Egypt	11,750	13,850,000
Italy	11,700	42,850,000	Chile	11,600	28,200,000
Pakistan	11,050	11,150,000	Bulgaria	10,050	14,500,000
Spain	9100	27,650,000	Singapore	9600	56,600,000
UK	7650	27,000,000	Morocco	8000	13,300,000
Singapore	6300	50,600,000	Pakistan	7800	4950,000
Total	326,300	978,150,000	Total	344,400	893,400,000

Figures based on commodity group pharmaceutical plants (SITC.3: 292.4 = HS 1211). Export figures include re-export. The quantities are given in tonnes (t). The main trade centers are underlined gray. *Source* UNCTAD COMTRADE database, United Nations Statistics Division, New York (*Source* Lange 2004)

plants amounted on average to 400,000t valued at USD 1224 million. The international trade is dominated by only few countries. About 80% of the worldwide imports and exports are allotted to only 12 countries with the dominance of temperate Asian and European countries. Japan and the Republic of Korea are the main consumers of pharmaceutical plants, and China and India are the world's leading producing nations; Hong Kong, the USA, and Germany stand out as important trade centers. Until now, the production of botanicals relies to a large degree on wild collection (Table 9.5).

Traded forms of botanicals

The plant raw material in trade consists of mainly dried plant parts, roots, leaves, bark, wood, flowers, or seeds, or sometimes, of several plant parts or even the whole plant if the demanded constituents are concentrated in several plant organs or even in the whole plant body. To a small extent, the plant material is traded fresh or preserved in alcohol (Lange 1996). The bulk of traded plant material is not or only little processed, which is in general cheaper than that which has been further processed, i.e., cut, rubbed, powdered, or even extracted.

Major traded botanicals

There are no or only few reliable trade data available for single botanicals (Lange 1996, 1998). The commodity group pharmaceutical plants include those used only in small quantities as well as bulk material with great industrial importance. In Germany, the most used medicinal plant is Gingko (*Gingko biloba*), followed by i.

a. Horse-chestnut (*Aesculus hippocastanum*), Hawthorn (*Crataegus* spp.), St John's-wort (*Hypericum perforatum*), Nettle (*Urtica dioca*), Echinacea (*Echinacea* spp.), Saw Palmetto (*Serenoa repens*), and Milk Thistle (*Silybum marianum*) (Grünwald and Büttel 1996). Some of these plants are also highly used in the USA, like Echinacea, St John's-wort, and Saw Palmetto, but the preferences are somewhat different: Siberian Ginseng (*Eleutherococcus senticosus*), Goldenseal (*Hydrastis canadensis*), Cat's claw (*Uncaria species*), Astragalus membranaceus, Dong Quai (*Angelica sinensis*), and Cascara Sagrada (*Rhamnus purshianus*) are listed among the top-selling botanicals (Laird 1999).

9.5 Herbal Wealth and Its Role in National Economy

Medicinal and aromatic plants, culinary herbs, etc., constitute an important natural wealth, the herbal wealth, of a country. It is estimated that up to 70,000 species are used in folk medicine (Farnsworth and Soejarto 1991), and over 21,000 plant taxa used for medicinal purposes (Groombridge 1992). According to the World Health Organization (WHO), about 25% of modern medicines are developed from plants sources used traditionally; and research on traditional medicinal herbal plants leads to discovery of 75% of herbal drugs (Mian-Ying et al. 2002). Traditional medicines derived from medicinal plants are used by about 60% of the world's population (Modak et al. 2007). They are important because they (a) play a significant role in providing primary health-care services to rural people; (b) serve as therapeutic agents as well as important raw materials for the manufacture of traditional and modern medicine; (c) serve as an income generating source of the rural people; and (d) substantial amount of foreign exchange can be earned by exporting medicinal herbs to other countries. In this way, indigenous medicinal herbs play significant role in health sector as well as in economy of a country. Bioactive compounds from medicinal plants can be directly used as healing agent and their phytochemicals also serve as lead compound for developing potential drugs to cure various diseases in human (Kamboj 2000; Verma and Singh 2008). Herbal preparations at present are known as alternative medicines. It has attracted increased attention of national media, policy makers, medical communities, government as well as non-government organizations all over the world largely because of the iatrogenic effects (adverse effects or complications) of the modern medicine. The World Health Organization also encouraged developing countries to use traditional plant medicines to fulfill a need unmet by modern system. The use of botanical raw material is in many cases much cheaper than to use chemical alternative substances. As a consequence, there is an enormous demand in botanicals in national and international arena resulting in a huge trade, on local, regional, national, and international levels. Diversity, flexibility, easy accessibility, broad continuing acceptance in developing countries and increasing popularity in developed countries, relative low cost, low levels of technological input, relative low side effects and growing economic importance are some of the positive features of traditional

medicine (WHO 2002). In the recent past and also in this first decade of the 21st century, there has been a growing interest in Traditional/Complementary and Alternative Medicine (TCAM) and their relevance to public health both in developed and developing countries. Traditional medicine refers to health practices, approaches, knowledge and beliefs incorporating plant-, animal-, and mineral-based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose, and prevent illnesses or maintain well-being and the term 'complementary' and 'alternative' medicine (non-conventional or parallel) are used to refer to a broad set of healthcare practices that are not part of country's own tradition, or not integrated into the dominant healthcare system Traditional medicine refers to health practices, approaches, knowledge and beliefs incorporating plant-, animal-, and mineral-based medicines, spiritual therapies, manual techniques and exercises, applied singularly or in combination to treat, diagnose and prevent illnesses or maintain well-being. TCAM is practice almost worldwide, and often it is called in various ways such as traditional medicine, alternative medicine, complementary medicine, natural medicine, herbal medicine, phytomedicine, non-conventional medicine, indigenous medicine, folk medicine, ethno medicine, etc. Chinese medicine, Ayurveda, Herbal medicine, Siddha, Unani, Kampo, Jamu, Thai, Homeopathy, Acupuncture, Chiropractic, Osteopathy, bone-setting, spiritual therapies, are some of the popular, established systems. However, there is no homogenous body of medical thought and practice which can be put under one name (Van der geest 1997; Patwardhan 2005).

Herbs includes entire plant, plant parts (leaves, flowers, fruits, seeds, stems, wood, bark, roots, rhizomes, or other plant parts in entire, fragmented, or powdered form), fresh juices, gums, fixed oils, essential oils, resins, etc. Herbal-finished products include comminuted or powdered herbal materials, or extracts, tinctures and fatty oils of herbal materials and finished herbal products consist of herbal preparations made from one or more herbs (mixed herbal product). Finished herbal products and mixed herbal products may contain excipients in addition to the active ingredients. In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients that are not of plant origin (e.g., animal materials and mineral materials).

Phytopharmaceuticals, herbal remedies, dietary supplements, homeopathics, herbal teas, liqueurs, spirits, sweets, aromas, perfumes, cosmetics, coloring agents, varnishes, detergents, etc., constitute herbal products. They are produced by extraction, fractionation, purification, concentration, and by other physical or biological processes. They also include preparations made by steaming, roasting, or stir baking with honey, alcoholic beverages, or other materials. Finished herbal products consist of herbal preparations made from one or more herbs. If more herbs are used, the term mixed herbal product be used. Finished herbal products and mixed herbal products may contain excipients in addition to the active ingredients. The bitter taste of Campari is based on the common centaury (*Centaurium erythraea*), and the fenugreek (*Trigonella foenum graecum*) contains steroid-saponins which are extracted for use in oral contraceptives.

Asia covers about 30% of the earth's land area and has some most biologically diverse countries like China, India, Indonesia, Malaysia, and the Philippines with rich traditional knowledge on the use of plants for therapeutic purposes (Anonymous 2010). Christophe Wiart working in the School of Biomedical Sciences of the University of Nottingham (Malaysia Campus) studied the medicinal plants of India, Southeast Asia, and China and collected, identified and classified 6000 medicinal plants species and he is regarded as the most prominent authority in the field of Asian ethnopharmacology, chemotaxonomy, and ethnobotany (Wiart 2007). Widely used Chinese herbs like *P. somniferum*, *A. annua* and *Taxus brevifolia* produce morphine, artemisinin, and paclitaxel, respectively (Cao and Kingston 2009).

Many of the Asian medicinal plant species that yield high-value products include *Catharanthus roseus*, *R. serpentina*, *Cephaelis peruviana* and other spp., *Coptis chinensis* and other spp., *P. somniferum*, *Dioscorea* spp., *Panax ginseng*, *P. peltatum*, *A. vera*, *Commiphora caudate* and other spp., *Mentha arvensis*, *Ocimum sanctum* and other spp., *Cymbopogon cytratus*, *Plantago psyllium*, *A. indica*, *A. annua* and other spp., *Cassia* spp., *Psoralea* spp., *Chlorophytum borivilianum*, *Pogostemon cablin* and other pp., *Piper nigrum* and other spp., *Chrysopogon zizanioides* (Gupta and Chadha 1995; Ayensu 1996).

Some commonly used medicinal (plants with therapeutic activity), medicinal and culinary (plants with therapeutic activity that enhance culinary dishes), and others are nutricicals (they have no therapeutic effects but health-promoting value) are *Actinidia sinensis* (fever, skin used fruits), *Adansonia digitata* (asthma, toothache as oil), *A. vera* (healing as balm, pills, oil), *Agrimonia eupatoria (*digestion, sore throat as infusion, decoction), *Allium sativum* (heart, anti bacterial in cooking), *A. cepa* (tension, colds as oignon cuit, potage), *A. schoenoprasum* (digestion whole plant, infusion), *Althaea officinalis* (anti-inflammator as infusion), A*nethum graveolens* (stimulant, stomachic as infusion, condiment), A*nthemis nobilis* (stress as infusion, balm), *Archangelica officinalis* (cough, colds), *Arctium lappa* (dermatosis as compresses), *Arnica montana* (contusions, ecchymoses as cream, decoction), *Artemisia absinthium (*intestinal problems as infusion), *Bambousa* (arthritis as cooking), *Borrago officinalis* (emollient, purgative as infusion, oil), *Bryophyllum pinnatum* (joint pains, leaves are used), *Butyrospermum* (healing, hydration as chocolate, baume), *Buxus chinensis* (dry skin as huiles), *B. sempervirens* (hair loss as infusion), *Calendula officinalis* (skin irritation as infusion, salad), *Camelia sinensis* (as infusion), *Calluna vulgaris* (urinary infection as powder, capsules), *Centaurea cyanus* (irritation of eyes and ears as infusion, eye drops), *Cereus grandiflorus* (hypertension as infusion), *Cinchomae cortex* (antibacterial, analgesic as écorce, poudre), *Cinnamomum verum* stomach ache as infusion), *Citrus aurantium* (tonic as infusion), *C.* limonum (sore throat, nausea as jus et fruit, gélule), *Colchicum* (neuralgia as infusion, vin), *Daucus carota* (cholesterol as légume cru), *Echium vulagre* (purgative as infusion), *Crataegus oxyacantha* (anxiety, palpitations as powder, capsules), *Elletaria caramomum* (loss of appetite seed is used), *Elytrigia repens* (kidney problems as decoction), *Ephedra sinica* (nasal decongestant as gélule), *Eucalyptus* globulus (respiratory problems as infusion, baume), *F. vulgare* (stomach

ache as cuisine, infusion), *Fraxinus excelsior* (rheumatism as feuilles), *Gentiana lutea* (loss of appetite, fatigue as tonique), *Ginkgo biloba* (antispasmodic as infusion), *G. glabra* (dermatosis as infusion, poudre), *Hamamelis virginiana* (circulatory troubles as décoction, crème), *Hibiscus* (fat elimination as infusion), *Humulus lupulus* (anxiety, insomnia as infusion), *Jasminum* (colds, cough, dermatosis as infusion), *Lavandula officinalis* (nervousness, insomnia as huiles), *Leontopodium alpinum* (cough, skin as infusion, serum), *Malva sylvestris* (respiratory, ENT as infusion, feuilles), *Matricaria recutita* (flu as infusion), *Melissa officinalis* (anxiety, insomnia as infusion), *Menyanthes trifoliate* (loss of appetite as compresse, *O. basilicum* (digestion as infusion, cooking), *Olea europaea* (tonic, hydrating as huile, fruits), *Panax* ginseng (stimulant, tonic as poudre, ampoule), *Passiflora incarnate* (insomnia as infusion), *P. crispum* (hypertension as persil frais), *Parietaria* officinalis (cystitis as infusion), *Papaver rhoeas* (insomnia, cough as infusion), *Pimpinella anisum* (antispasmodic, sedative as infusion), *Pinus sylvestris* (respiratory problems as poudre, infusion), *Pogostemon cablin* (colds, migraines as huiles), *Rosa canina* (tonic, anemia as infusion, decoction), *Rubus idaeus* (intestinal problems as feuilles), *R. fruticosus* (oral complaints as decoction), *Rosmarinus officinalis* (healing, stimulant as infusion), *Salvia officinalis* (asthma, menopause as poudre, infusion), *Sambucus* (flu, fever as infusion, baume), *Spirea ulmaria* (analgesic as poudre, infusion), *Taraxacum* (kidney problems as infusion, salade), *Tilia platyphylos* (insomnia, inflammation as infusion), *Vaccinium oxycoccos* (urinary infections as infusion), *Verbascum* (cough as powder, capsules), *Viola tricolor* (purgative as poudre, infusion), *Viscum album* (arteriosclerosis, gout as jus, feuilles), *Vitis vinifera (*glowing skin fruits are used), *Z. officinale* (aphrodisiac, tonic as infusion, cuisine), *Glycine max* (anemia as cuisine), *Mentha spicata* (antispasmodic as poudre, infusion), *Hypericum perforatum* (depression as gélule, infusion), *Ortica dioica* (diuretic as infusion, potage), *Arbutus unedo* (diuretic as sirup), *Helianthus annuus* (headache, fever as graines, huile), *Origanum marjorana* (nausea as condiment), *Thymus vulgaris* fortifying as infusion), *Lycopersicon* (sunburn used fruit), *V. officinalis* (insomnia, anxiety as infusion), *Lippia citriodora* spasms, insomnia as infusion, feuilles), *Triticum* (skin, hair yeast, oil), *Thymus serpyllum* (gastric infections as infusion).

Natural excipients like coloring (*Curma longa*, *C. sativus*, *Carthamus tinctorius*, *Calendula officinalis*) and flavoring agents (*Mentha arvensis*, *Cymbopogon flexuosus*, *C. martini*, *Cyperus scariosus*, *E. globules*), emulsifying and suspending agents (*Plantago ovata*), diluents, bulking agents or filler (plant cellulose as well as lactose, sucrose, glucose, mannitol, sorbitol, calcium carbonate, and magnesium stearate) and disintegrants (carboxymethyl cellulose), anesthetic aids (*Cannabis sativus*, *P. methysticum*), sweeteners (*G. glabra*, *Stevia rebaudiana*), carrier for targeted drug delivery (e.g., pectins, agar, gelatin, wax, fixed oils), binders (non-starch polysaccharides-pectins, alginates and proteins-gelatin), adhesives (guar gum, amylase, and karaya gum), solidifiers (beeswax, cocoa butter, or theobroma oil), material for surgical dressings (natural fibers, filtering agents—diatomite, support media) yielding plants are also included within the herbal spectrum as pharmaceutic necessities. Natural excipients are stable, biodegradable,

inexpensive, easily available, and safe in contrast to their many synthetic counterparts.

Beverages like tea and coffee (*Camellia sinensis*, *Coffea arabica*), spices, and condiments like Cinnamon (*Cinnamum zeylnicum*) bark, cardamom (*Amomum aromaticum* and *A. subulatum*) fruit and various fruits of Apiaceae such as fennel (*F. vulgare*), coriander (*C. sativum*), cumin (*Cuminum cyminum*), anise (*Pimpinella anisum*, etc.); seeds of mustard (*Brassica alba*, *B. juncea*, *B. nigra*), flower-bud of clove (*Syzygium aromaticum*), and rhizome of ginger (*Z. officinale*) are some typical examples; poisonous (e*Abrus precatorius*, *A. belladonna*, *Colchicum autumnale*), hallucinogenic or psychoactive (*Cannabis sativa*, *Datura stramonium*, *Ipomoea purpurea*, *Salvia divinorum*) and teratogenic (*Datura stramonium*, *Lupinusformosus*, *Nicotiana glauca*, *Coniummaculatum*) plants, raw materials for the production of oral contraceptives (*Dioscorea alata*, *D. villosa*), aphrodisiacs (*Epimedium*, *Glycoirrhiza glabra*, *Smilax ornate*, *Turnaria aphrodisiaca*, ginger, ginseng, *Ginkgo biloba*), allergens, enzymes, vitamins, antibiotics, herbicides, and insecticides yielding plants remain within the arena.

Lange (2004) gave an elaborate enumeration on the herbal wealth of different countries and continent of the world. UNESCO (1996) has observed that the use of traditional medicine and medicinal plants in most developing countries is a normative basis for the maintenance of good health. The World Health Organization has estimated conservatively that between 60 and 90% of the population of the non-industrialized/developing countries rely (fully or partially) on medicinal plants to cure variety of aliments. Different estimates announced number of medicinal plant species that are used for medicinal purposes worldwide. Out of the total 250,000–500,000 plant species on earth (Borris 1996), more than 80,000 are known as medicinal plants and about 35,000–70,000 species are used medicinally across the world. According to an estimation by Farnsworth and Soejarto (1991) that up to 70,000 species are used in folk medicine while an enumeration of WHO from the late 1970s listed 21,000 medicinal species (Penso 1980) and now it is assumed that, out of the global total 422,000 flowering plant species, the number of plant species used for medicinal purposes across the world is >50,000 (Govaert 2001; Bramwell 2002; Schippmann 2002). However, only 1–10% of them have been studied chemically and pharmacologically for their potential medicinal value (Verpoorte 2000). The World Health Organization reported the use of over 21,000 plant taxa for medicinal purposes around the world (Penso 1980, Groombridge 1992). But how many plant species are used worldwide in cosmetics, spirits, or aromas are yet not known exactly. However, only 1–10% of them have been studied chemically and pharmacologically for their potential medicinal value (Verpoorte 2000). From a calculation based upon the estimated total number of about 35,000–70,000 species are used medicinally across the world, it is apprehended that at least every fourth plant is in use. The use of the number of medicinal and aromatic plant species in some regions of the world is quite impressive.

Bangladesh is rich in herbal resources because of its geographical location, fertile soil, and favorable subtropical monsoon climate. Bangladesh shows richness in greeneries with significant species diversity. Geographically, Bangladesh falls

near the Indo-Burma region which is one of the ten global hot-spot areas that supposed to have 7000 endemic plant species (Mittermeier et al. 1998). Bangladesh has been the abode of more than 6000 higher plant species, of which about 300 are exotic and 8 are endemic. Of the total number of plant species, there are 5000 angiosperms, 4 gymnosperms, 250 Pteridophytes including 230 ferns, 250 Bryophytes. About 300 species and varieties of algae have been recorded from freshwater habitats alone and many more grow in brackish and sea water habitats (Banglapedia 2003). A total of 334 species of higher plant species (Spermatophytes and Pteridophytes) were identified from the Sundarbans forest and along the 710-km-long coastline of the Bay of Bengal. About 168 species of seaweeds from the Bay are also known. In Bangladesh, more than 5000 higher plant species grow (Mia 1990), and about 1000 plant species (20%) are considered to have medicinal properties. At least 177 species and a variety of orchids under 70 genera of the family Orchidaceae grow in Bangladesh (Huda 2007). Most of the identified 5000 angiosperms in Bangladesh grow wild in nature, and only 210 species are cultivated for flowers, food, fodder, fiber, beverage, medicine, and timber. About 455–747 plant species of Bangladesh have been described with their specific medicinal properties (Ghani 2003; Yusuf et al. 2009). Many of these medicinal plants grow in the wild but some of them are garden plants and some them are cultivated crop species. Most of this floral wealth of Bangladesh is used in the indigenous systems of medicine, particularly Ayurveda, Unani, and Homeopathy medicine as well as folk medicine.

In India, more than 45,000 different plant species grow and out of them, about 15,000–20,000 plants (3.3–4.4%) have good medicinal value. However, only 7000–7500 species are used by traditional communities for medicinal purposes (Joy et al. 1998). Earlier, Shankar and Majumdar (1997) reported that out of the 17,000 Indian native plant species, about 7500 species are used in ethnomedicines, and Grover et al. (2002) reported that many traditional medicines used in India are derived from medicinal plants, minerals, and organic matter. In India, the largest producer of medicinal herbs (so the botanical garden of the world), grows about 2500 species out of the world 21,000 enlisted medicinal plants of the World Health Organization and out of which 150 species are used commercially on a fairly large scale (Seth and Sharma 2004). Modak et al. (2007) prepared a list of Indian medicinal plants with proven antidiabetic and related beneficial effects including *Allium sativum*, *Eugenia jambolana*, *Momordica charantia*, *Ocimum sanctum*, *Phyllanthus amarus*, *Pterocarpus marsupium*, *T. cordifolia*, *Trigonella foenum graecum,* and *W. somnifera*. In Nepal, 6653 species of Angiospermic plants were documented among which 1792–2331 were recorded as potential medicinal and aromatic plants (Rokaya et al. 2010). The two ethnic groups Magar and Majhi of Nepal use ethnobotanically 132 plant species of 67 families and 99 genera against 12 human ailments. The herbs were the primary sources of medicine 87 (66%), followed by shrubs 26 (20%), trees 11 (8%), and climbers 8 (6%) in Parbat district of Nepal (Mallaa et al. 2015). Widely used medicinal plant species of Nepal include *Paris polyphylla*, *Bergenia ciliate*, *Swertia chirayita*, *Potentilla polyphylla*, *Zanthoxylum acanthopodium*, *Centella asiatica*, *Camellia kissi*, *Benincasa hispida*,

Valeriana hardwickii, *Cuscuta reflexa*, *B. aristata*, *Bryophyllum pinnatum*, *Tinospora sinensis*, *Dendrobium moschatum*, *Nephrolepis auriculata*, *Vitex negundo*, *Wikstroemia canescens*, *Acampe papillosa*, *Indigofera bracteata*, *T. wallichiana*, *Zizyphus mauritiana*, *Spiranthes sinensis*, *Sambucus adnata*, *Chlorophytum nepalense*, *Neolitsea pallens*, *Coelogyne corymbosa*, etc. (Mallaa et al. 2015).

The number of medicinal plant species used in China is about 6000 (Xiao 1991) but may be over ten thousand according to another source of estimation (He and Ning 1997). In China, 4941 of 26,092 native species (18.9%) are used as drugs in traditional medicine (Duke and Ayensu 1985). It is thought that approximately 1000 plant species are commonly used in Chinese medicine, and about half of these are considered as the main medicinal plants (He and Ning 1997). The traditional medicine of eastern Asia, the traditional Chinese medicine (TCM), relies in most cases on indigenous plant species. Following TCMT, the Japanese established Kampo medicine prepared following Kampo formulae. Under the Japanese law, products with nutritive function (e.g., vitamins, minerals) and without therapeutic activities are traditionally considered as foods (e.g., soybean, tea, psyllium, wheat, guava, coffee, Eucommunia bark, seaweed, sesame seed, broccoli, cabbage). Crude drugs must meet at least 13 Japanese pharmacopoeia (JP) criteria (e.g., name, origin, medicinal part, preparation process, content of specific constituents, description, identification, purity including heavy metals, arsenic, residual pesticides, loss of drying, total ash, acid-insoluble ash, extract content, assay) to qualify as medicine. In 2001, 121 crude drug species and their 52 powdered forms were listed in JP 14th edition. However, revisions and new advances from the non-JP crude drug standards (internal regulations for approval) after 2006 led to the addition of Supplement I in JP 15 in 2007 which expanded the list to 153 crude drugs and their 54 powdered forms. Medicinal plants in the Republic of Korea present concise monographs of 150 medicinal plant species that are most commonly used for medicinal purposes in traditional Korean medicine of the Republic of Korea.

The Japan Kampo medicines manufacturer association (JKMA) most frequently uses 150 crude drugs for medicine and food (Anonymous 2006). The most commonly used drugs are Ginger, Coix seed, Capsicum, turmeric, Glycyrrhiza, cinnamon bark, Cassia seed, safflower, Angelica, Astragalus, Phellodendron, Coptis, Rhubarb, Aconite, bamboo grass, Zedoary, Cnidium rhizome, Artemisia, Zanthoxylum fruit, etc. Japan, however, imports a bulk quantity of medicinal and non-medicinal crude drugs in 2002 (import—56,221t, domestic cultivation 1723t) from China (58%), Thailand (19%), India (13%), Sudan (2%), and Taiwan (1%) (Anonymous 2007). Wiart (2012) in his book 'Medicinal Plants of China, Korea, and Japan: Bioresources for Tomorrow's Drugs and Cosmetics' provides an elaborate conceptual tools and understanding of intercorrelated basics of botany, ethnopharmacology, biomolecular pharmacology, phytochemistry, and medicinal chemistry to guide researchers in appreciating, estimating, and forecasting the pharmacological or cosmetological value of Asian medicinal plants with emphasis on numerous patentable pharmaceutical and cosmetological leads. Detailing 200

medicinal plant species carefully selected for their potential importance in pharmacological and cosmetological importance, Wiart opined that the Asian medicinal plants have great promise in pharmaceutical and cosmetological development.

Medicinal herbs are used in Philippines as an economical alternative medicine to treat many ailments (e.g., from boils to body odor) which is beneficial to many Filipinos, especially in the economic crisis. Common practices of herbal healing in Philippines are boiling of fruits and flowers, extraction of juices from leaves, and poultices from barks and roots. For this, at least 75 medicinal plants including cultivated and wild plant species of Philippines are in use, e.g., *Abelmoschus esculentus*, *Allamandra cathartica*, *Allium sativum*, *ALoe barbadensis*, *Amaranthus spinosus*, *Ananas comosus*, *Andropogon citratus*, *Anona reticulate*, *Anona squamosal*, *Areca catechu*, *Artocarpus heterophylla*, *Auerrhoa carambola*, *Basella rubra*, *Biva orillan*, *Blumea balsamifera*, *Brassica oleracea*, *Cassia alata*, *Cassia fistula*, *Carica papaya*, *Centella asiatica*, *Chrysanthemum indicum*, *Chrysophyllum cainito*, *Coeus blumei*, *Croton tiglium*, *Curucuma domestica*, *D. metel*, *Daucus carota*, *Jatropha curcas*, *Nerium Indicum Mil*; *Premna Odorata*, *Portulaca olearacea L.*; *Tagetes erecta Linn*; *Momordica charantia*, *O. basilicum*, *Ficus stipulosa Miq. Linn.*; *Lagerstroemia speciosa*, *Psidium guajava*, *Piper beetle.*; *Theobroma cacao.*; *Symphytum officinale*; *Syszygium jambolanum*; *Kaempferia galanga*; *Entada phaseikaudes*; *Hibiscus rosa-sinensis*; *Mentha cordifolia*; *Leucaena glauca*; *Gliridia sepium*; *Plumeria acuminata*; *Impatens balsamina*; *Pithecolobium dulce.*; *Hedychium coronarium*; *Manihot esculenta*; *Ipomea aquatica*; *Lantana camara*, *Kalanchoe pinnata*; *Imperata cylindrica.*; *Vitex negundo*, *Raphanus sativus*, *Tinospora rumphii*, *Mimosa pudica*, *M. oleifera*, *Mangifera indica*, *Quisqualis indica*, *Coleus aromaticus*, *Tabernaemontana pandacaqui*, *Pandanus odoratissimus*, *Luffa acutangula*, *Ros marinus officinalis*, *Tamarindus Indica*, *Pachyrrhizus erosus*, *N. tabacum*, *Solanum melongena*, *Polymnia sanchifolia*; *Zea mays*, *Z. officinale*, *Below are links to certain kinds of illness with corresponding herbal treatments.* One or more these herbs in combination are used to prepare home remedy to treat many diseases such as boils, chronic cystitis, asthma, bee sting, bleeding from wound,, burns, chicken pox, constipation, cough, dandruff, diarrhea, eczema, fainting, fever, flatulence, fractures, sinusitis, hemorrhoids, herpes, hyper-acidity, indigestion, head lice, skin rashes, mosquito bites, mumps, acne, arthritis, scabies, ringworm, dermatitis, dry itchy skin, snake bites, throat sore, ankle sprain/wrist sprain, sunburn/prickly heat, stomatitis/gum sore, toothache, body odor, worm infestation.

Traditional healers in many African countries rely on local or at most regional plant material (Marshall 1998). Over 5000 plant species are known to be used for medicinal purposes in Africa (Iwu 1993), while about 2000 medicinal and aromatic plant species are used on a commercial basis in Europe as it has a long tradition in the use of botanicals (Lange 1998). The use of medicinal and aromatic plant species in Germany would be not less than 1500 (Lange 1996) and that of Spain would be 800 medicinal of which 450 species are associated with commercial use (Lange 1998). In Bulgaria, about 750 native plant species, 20% of the total flora, are used in folk medicine. Of these, 200–300 species are most commonly used (Hardalova 1997).

In Albania, 205 native plant species are used as sources of botanicals (Lange 1998). In Hungary, some 270 native medicinal and aromatic plant taxa are used, 180–200 of which are officially recognized by the Hungarian pharmacopoeia as cited by Lange (2004). Lange (1998) from the French pharmacopoeia and lists of medicines noted some 900 taxa, of which almost half are native to Europe.

Herbs used in a country can be either indigenous or native to other regions or even continents. The share of both plant groups depends on the country's cultural preferences, importance of traditional medicines, history, trade relations, and of course of the wealth or property of a country. Traditional medicines are playing an important role in many parts of the world. In south and Southeast Asia, the Ayurveda, Unani, and Siddha medicines are widely distributed and based on not less than 400, 500, respective 1800 native Indian plant species (Shankar and Majumdar 1997). The TCM, the traditional medicine of eastern Asia, relies in most cases on indigenous plant species. Traditional healers in many African countries rely on local or at most regional plant material (Marshall 1998). In Bulgaria, about 750 native plant species, or 20% of the total flora, are used in folk medicine. Of these, 200–300 species are most commonly used (Hardalova 1997). Further, in Albania, 205 native plant species are used as sources of botanicals (Lange 1998). In Hungary, some 270 native medicinal and aromatic plant taxa are used, 180–200 of which are officially recognized by the Hungarian pharmacopoeia (Lange and Schippmann 1999). In Turkey, about 337 native taxa have been commercially traded since at least 1990 (Lange 2001). From the French pharmacopoeia and lists of medicines (Lange 1998) noted some 900 taxa, of which almost half are native to Europe. This means, that many countries rely on a major part on their own plant diversity. Many of them cannot afford to import foreign botanicals, finished herbal products, or even phytopharmaceuticals, and the country's own 'biodiversity' is mainly offered in a crude form or at most as little processed products on the market. On the other side, there are the developed countries which use besides indigenous plant species a lot of non-native species and process them in their well-developed pharmaceutical, cosmetic, and extract-producing industry. Accordingly, the plant material is offered to the consumers as mainly packed and finished products, and the crude material plays a minor role in the retail trade. This features apply above all to the highly industrialized countries of temperate Asia (e.g., Japan and the Republic of Korea), of the Americas and of Europe. The geographical origin of the botanicals used in Germany may illustrate the kind of use of non-native and native species (Lange 1996). In general, the medicinal and aromatic plants are coming from all geographical regions of the world, and many of these species show a wide geographical range. The high figure of 849 species occurring in temperate Asia are increasingly used in Germany, and many of the 454 species grow in North America are used in homeopathy. Species with their distribution area restricted to Africa, South America, Australia, New Zealand, or the Pacific play a minor role in Germany's industry. A high number of not less than 605 species are native to Europe. The majority of them are distributed across several geographical units, e.g., Eurasia or even the northern hemisphere; only 16 species are limited to Europe. Many of the 605 species are growing in Mediterranean countries like Italy, France,

Spain, and Greece, and more than two-thirds of them occur in east and southeast Europe, in Romania (451 species), Bulgaria (421 species), Hungary (415 species), Albania (391 species), and in Poland (386 species). In general, both regions are rich suppliers for botanicals within Europe (Lange 2001).

Threats and Conservation Aspects

Threats facing medicinal and aromatic plants and their wild populations are (1) the intensive and increasing commercial collection, often concentrated in few areas, (2) the largely unmonitored trade, (3) destructive harvesting techniques, (4) trade structure changes in countries of the former Eastern Bloc, and (4) global habitat loss and alteration. During the 1990s, the demand in raw material increased due to the increasing demand in plant-based remedies and products—a result of the increasingly global nature of the trade, the worldwide population growth and the increasing popularity of herbs and herbal products in industrial nations and their effective marketing. This has resulted in some countries, above all in the USA and Japan, in explosive demand and consumption of medicinal plants (Laird 1999); in particular, the demand in St. John's-wort increased by several hundred percent in the USA in the middle of the 1990s. Additionally, more and more people in industrialized countries are increasingly interested in foreign traditional medicines like Ayurveda and TCM. In all, the imports of pharmaceutical plants increased from about 270,000t in 1991 to almost 400,000t in 2000. In general, on regional and country levels, the imports increased until 1996–1998, sometimes considerably as in the case of the temperate Asian countries. Between 1996 and 1998, the market in pharmaceutical plants broke down in particular in the USA and in temperate Asia, but has already started to recover. In many of the major supply countries of botanicals, the exports have increased significantly in the 1990s. In China, the exports of pharmaceutical plants doubled almost from 107,500t in 1991 to 186,450t in 2000, and the domestic demand for botanicals has grown at an annual rate of 9% over the past decades (He and Ning 1997). Also, Europe has doubled its export during this period, and Mexico has shown very high export increases since the mid-1990s.

9.5.1 Conservation Concepts and Management of Botanical Resources

In the case of medicinal and aromatic plants, conservation concepts and management measures have to meet both (1) future supply and (2) the provisions of species conservation. Measures to be taken on local, regional, national, or international ranging from resource management, cultivation, adequate species conservation programmes, and shifting processing from consumer to source countries, to trade restrictions or even trade bans. In the following, some selected conservation aspects

and resource management issues will be briefly discussed. According to IUCN, WHO, and WWF (1993), the cultivation of medicinal and 187 aromatic plants is the best and promising way to satisfy the market's expanding demand for these raw materials. But, up to now, cultivation has not proved to be profitable for the majority of taxa in trade (Lange 1998): (1) Many plants are difficult to cultivate, (2) to take a plant into cultivation, if possible, will often last many years, (3) many plants are only required in small quantities, (4) in some cases the quality of wild-harvested material is supposed to be superior, and (5) the costs for wild-crafted plant material are in general lower than for cultivated material (Lange 1997).

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Chapter 10
Herbal Drugs: Their Collection, Preservation, and Preparation; Evaluation, Quality Control, and Standardization of Herbal Drugs

Abstract The WHOs' criteria for good herbal drug preparation include the identity of source plant, optimum time of harvest, post-harvest handling, cooking utensils etc. Natural drug products may be obtained from the wild or through cultivation, fermentation, cell or organ culture, microbial transformation as well as biologics. Right source of drug plant and harvest time are important factors for maximizing the yield of the desired phytochemical content. Collection schedule of different plant parts are different, e.g., roots and rhizomes at the end of the vegetation period, bark in the spring, leaves and herbs at bloom, flowers at anthesis or shortly after opening, and fruits and seeds after maturity or ripe. Hand collection is preferable for wild source. Post-harvest handling including garbling, washing, drying in air, oven drying, milling and re-milling, sieving, storage, labeling with the name of the plant, place and date of collection are important for standard herbal preparation. Collected plant material must be preserved to keep the active compounds unchanged during transport and storage. Drying, freeze-drying or lyophilization, stabilization, fermentation etc. are some of the common methods of preservation. Herbal preparations are made from herbal drugs, such as whole plant, plant parts, algae, fungi, lichen, exudates, in a crude state in dried or fresh form and extracts with the help of different processes such as infusion, decoction, maceration, distillation, expression, fractionation, purification, concentration, fermentation. These herbal preparations include whole plant or parts, comminuted or powdered herbal drugs, tinctures and extracts, fatty oils, essential oils, expressed juices and processed exudates of herbal materials. Herbal preparations are the basis for finished herbal products. Finished herbal products are medicinal products containing exclusively herbal drugs (active substances) and herbal drug preparations. They also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey, or in other materials and may consist of herbal preparations made from one herb or more herbs (mixed herbal product). They may contain excipients in addition to the active ingredients or may contain natural organic or inorganic active ingredients not of plant origin (e.g., animal materials and mineral materials). Finished products or mixed products to which chemically defined active substances have been added, including synthetic compounds and/or isolated constituents from herbal materials, are not considered to be herbal. Herbal drugs are precisely defined by the botanical

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scientific name according to the binominal system. Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products. Storage of crude drugs in dry condition in airtight container placed in dry dark place is very important for stability and quality maintenance. Grinding of crude drugs by hammer-, knife- or tooth mill to a powder of suitable particle size is carried out for isolation of a pure compound or for manufacture of a simple preparation. Cold grinding is preferable for crude drugs containing heat labile compounds. Sifting to ensure particle size (course—2.00 mm to fine—0.18 mm) can be performed following the principles of sieving and blast sifting. Extracts are preparations of crude drugs containing all the constituents soluble in the extracting solvent. Extracts may be dry (when all solvent has been removed), soft or fluid (solvent prepared with mixtures of water and ethanol). Tinctures are prepared by extraction of the crude drug with five to ten parts of ethanol of varying concentration without concentration of the final product. For both extracts and tinctures the ratio drug to solvent should always be stated. The criteria for ideal solvent for a certain pharmacologically active constituent include high selectivity for the compound to be extracted, high capacity for extraction in terms of coefficient of saturation of the compound in the medium, nonreactive with the extracted compound or with other compounds in the plant material, low price, harmless to man and to the environment, completely volatile. Aliphatic alcohols (up to 3C) or mixtures of the alcohols with water, are the solvents with the greatest extractive power for almost all natural substances of low molecular weight such as alkaloids, saponins, and flavonoids. Ethyl alcoholis used for obtaining tinctures and fluid, soft and dry extracts. The ethanol–water mixture induces swelling of the plant particles and increases the porosity of the cell walls and thus facilitates the diffusion of extracted substances. For extraction of barks, roots, woody parts and seeds the ideal alcohol: water ratio is about 7:3 or 8:2. For leaves or aerial green parts the ratio 1:1 is usually preferred in order to avoid extraction of chlorophyll. Herbal internal preparations include infusions, decoctions, tinctures, macerations, percolation, digestion, inhalation of powdered plants, steam inhalation, aromatherapy, dry preparations etc. and washes, compresses, poultices, salves and balms are the main external preparations. Infusions are made with leaves and flowers, while decoctions are made with roots, bark, seeds, and berries. Infusion and decoction are preferred for water soluble chemicals (e.g., anti-inflammatory plant steroids) while tincture for alcohol soluble chemicals (anti-bacterial alkaloids). This may explain why a tea of the plant is used for arthritis while a tincture is traditionally used to treat various bacterial infections. Several problems influence the quality of herbal drugs. Quality control and the standardization of herbal medicines involve several steps. The source and quality of raw materials, good agricultural practices and manufacturing processes are certainly essential steps for the quality control of herbal medicines and play a pivotal role in guaranteeing the quality and stability of herbal preparations. For standard herbal drug production at industrial level, source herbal ingredients should be analyzed in detail in respect of quality, efficacy, performance and safety because drugs in commerce are frequently adulterated and do not comply with the standards prescribed for authentic drug. Quality refers to the status of a drug and is based on

three important pharmacopoeial definitions such as identity, purity, and content of active constituents. Voucher specimens are reliable reference sources. Purity evaluation includes ash values, contaminants, heavy metals, microbial contamination, aflatoxins, radioactivity, and pesticide residues. Analytical methods, such as photometric analysis, TLC, HPLC, GC, MS or GS/MS, can be employed to establish the constant composition of herbal preparations. For content, sometimes markers can be used for control purposes because in most herbal drugs the active constituents are unknown. In other cases, where no active constituent or marker can be defined for the herbal drug, the percentage extractable matter with a solvent may be used as a form of assay. The choice of the extracting solvent depends on the nature of the compounds involved, e.g., hot water for herbal tea, steam distillation is suitable for essential oils. Complex nature of herbal drugs, unknown active principle, unavailability of selective analytical methods or reference compounds, chemical and natural variability in the plant materials as well as in source and quality of the raw material, methods of harvesting, drying, storage, transportation, and processing etc. are some of the problems that influence the quality of herbal drugs. Strict guidelines have to be followed for the successful production of a quality herbal drug. Standardization involves adjusting the herbal drug preparation to a defined content of a constituent or a group of substances with known therapeutic activity by adding excipients or by mixing herbal drugs or herbal drug preparations because botanical extracts made directly from crude plant material show substantial variation in composition, quality, and therapeutic effects. Standardized extracts are high-quality extracts containing consistent levels of specified compounds, and they are subjected to rigorous quality controls during all phases of the growing, harvesting, and manufacturing processes. Evaluation of crude drug means confirmation and determination of its identity, quality and purity and it can be done by several methods viz. organoleptic and microscopic evaluation; analytical determination of foreign matter, plant ash, heavy metals, microbial contaminants and aflatoxins, etc. Potentially hazardous contaminants and residues in herbal medicines may be grouped as chemical, biological, agrochemical residues, residual solvents, etc.

Keywords Collection · Preservation · Herbal preparations · Analytical evaluation · Quality control · Standardization of herbal medicines

10.1 Herbal Drugs, Their Collection and Preservation

Drug evaluation includes may the determination of identity, purity, and quality of a drug. Identity of biological source, the quantity of the active constituents and the extent of foreign organic material present in a crude drug determine its quality and standard. Pharmaceutical quality of medicinal product is the basis for ensuring safe and effective medicines. Herbal drugs are mainly whole plant, plant parts (e.g., leaves, flowers, fruit, seeds, stems, wood, bark, roots, rhizomes, or other plant

parts), algae, fungi, lichen in an unprocessed state (crude state), in fresh, dried, entire, fragmented or powdered form. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal drugs. Herbal drugs are precisely defined by the botanical scientific name according to the binominal system. Herbal preparations and finished herbal products are also included in herbal medicines. Herbal drugs are obtained from cultivated and wild sources. Suitable collection, cultivation, harvesting, drying, fragmentation, and storage conditions are essential to guarantee the quality of herbal drugs. Herbal drugs are, as far as possible, should be free from impurities such as soil, dust, dirt, and other contaminants such as fungal, insect, other animal contaminations, and rotten plant parts. Decontaminating treatment, if used, should not affect the active drug constituents and should be free from residual effect. The use of ethylene oxide is prohibited for the decontamination of herbal drugs. In the EU, a complex regulatory framework exists that encompasses specific requirements for herbal medicinal products and for marketing, requires authorization by the competent authorities (Kroes 2014). The basic principles governing the assurance of the quality of medicinal products are defined in the amended Directive 2001/83/EC and Directive 2003/63/EC.

The phytochemical composition of plant is variable because of inherent variability and a plethora of external factors, so the production process of quality herbals needs strict systematic regulation. The source materials need to be correctly authenticated and free of adulterants and contaminants. In addition, proper harvest (season and time, developmental stage, temperature, and humidity) and post-harvest processing (drying and storage) have a strong impact on metabolite production plant and alteration of the phytochemical composition of herbal material, respectively. For extraction, the solvent as well as conditions need to be optimized in order to enrich the bioactive constituents in the extract; quality of finished preparations needs to be determined either on the basis of marker constituents or on the basis of analytical fingerprints by applying different methods ranging from macroscopic, microscopic, and DNA-based authentication methods to spectroscopic methods such as vibrational spectroscopy and chromatographic and hyphenated HPLC, GC–MS, and LC–MS methods (Pferschy-Wenzig and Bauer 2015).

According to WHO (2007), herbal preparations are the basis for finished herbal products and may include comminuted or powdered herbal materials, or extracts, tinctures, and fatty oils, expressed juices and processed exudates of herbal materials. They are produced with the aid of extraction, distillation, expression, fractionation, purification, concentration, fermentation, or other physical or biological processes; and also include preparations made by steeping or heating herbal materials in alcoholic beverages and/or honey or in other materials. The finished herbal products or herbal drug preparations are medicinal products that contain exclusively herbal drugs (active substances), may be made from one herb or more herbs (mixed herbal product) and may contain excipients in addition to the active ingredients. In some countries, herbal medicines may contain, by tradition, natural organic or inorganic active ingredients, which are not of plant origin (e.g., animal

materials and mineral materials). Finished products or mixed products to which chemically defined active substances have been added, including synthetic compounds and/ or isolated constituents from herbal materials, are not considered to be herbal.

WHO's Guidelines for Quality Drugs

Some guidelines formulated by the World Health Organization (WHO 2007) on the use of medicinal plants (proper identity of the medicinal plants), harvest (right time schedule), post-harvest handling (garbling, washing, drying, milling, storage etc.), pottery or pots as cooking utensils (glass, ceramic pot as cooking utensils; copper and stainless steel pot can also be used but not pots made of aluminum, iron, tin or other metals), etc. related to herbal drug preparation are described in the following paragraphs.

Natural drug products may be obtained through collection (wild), cultivation (commercial), fermentation (recombinant DNA technology or genetically engineered drugs), cell culture techniques, microbial transformation as well as biologics (prepared from the blood of animals). Proper botanical identity of the medicinal plants is necessary for ascertaining the right source of drug. Choice of time suitable for collection in an important factor because the amount of a constituent is usually not constant throughout the life of a plant, the stage at which a plant is collected or harvested is, therefore, very important for maximizing the yield of the desired constituent, and the differences are sometimes not only quantitative but also qualitative.

i. **Collection**

Adherence to good agricultural and collection practices (GACP), good plant authentication and identification practice (GPAIP), good manufacturing practice (GMP) before and during the manufacturing process and good laboratory practice (GLP) in analysis are necessary for quality herbal products and their safety and efficacy (Govindaraghavan and Sucher 2015). Suitable time for collection of herbal materials is important for maximizing plant biomass yield, quantitative and qualitative constituents. The optimum time for collection of a plant or its part is necessary to coincide with its optimal state of development and phytochemical content, e.g., roots and rhizomes—at the end of the vegetation period, bark—in the spring, leaves, and herbs—when plant is about to bloom, flowers—just before or shortly after opening, and fruits and seeds—when fully ripe. Hand collection of medicinal plants is preferable and this is especially true in the case of wild plants. With cultivation on a large scale, it may be possible to use modern agricultural harvesters, but in many cases, e.g., barks, manual collection is unavoidable. Thus, the cost of drug production is largely the cost of the labor involved. Post-harvest handling includes garbling—separation and removal of unwanted materials from plants itself or from dirt and other foreign matters, washing—flushing away of soil and/or other solid particles by a thorough but fast rinse with clean running water quickly (long exposure to water may affect the active constituents), drying air (in shaded under ventilation until crumbly, chopped into small pieces if succulent),

oven drying (with circulating air at temperature at not higher than 60 °C), milling and re-milling (reduction to the required particle size as specified), sieving (for uniformly sized particles), Storage—in plastic containers or bottles, preferably brown colored with tight cover away from sunlight in cool place, added charcoal for maintaining dryness, container labeled properly with the name of the plant, date place and date of collection, well-dried and well-stored plant materials can be used up to 6 months after the collection, not to be used older materials and materials with molds or other signs of decay, etc.

After collection, the plant material must first be preserved so that the active compounds will remain unchanged during transport and storage. The cells of living plants contain large number of low molecular weight compounds and enzymes, and the cells have many kinds of barriers that keep these constituents apart. When the plant dies the barriers are quickly broken down and the enzymes get the opportunity to promote various chemical changes in the cell constituents (e.g., oxidation, hydrolysis). Different methods of preservation aim at limiting these processes as far as possible.

ii. **Drying**

Drying is the most common method for preserving plant material is drying. Like many other crops, medicinal plants have to be dried before storage. Drying is defined as decreasing moisture content (MC) to preserve the product for extended shelf life. MC is commonly defined either as mass of water *mw* per total mass noted as MC wet basis (wb) in percentage. Microbes such as fungi, yeasts, and bacteria increasingly develop at >70% relative humidity (RH) and since the activity of decomposing enzymes is also enhanced by increasing water activity, a threshold of RH $\leq$ 60% is recommended to preserve the quality of medicinal plants during storage (Müller and Heindl 2006). The final MC to which the material should be dried can be derived from the sorption isotherm as depicted by Heiss and Eichner (1990). Living plant material has high water content: leaves may contain 60–90% water, roots and rhizomes 70–85%, and wood 40–50%. The lowest percentage, often no more than 5–10%, is found in seeds. Enzymatic breakdown takes place in moist condition and rapid removal of the water from the cell will, therefore, largely prevent degradation of the cell constituents. To stop the enzymatic processes, the water content must be brought down to about 10%. Drying also decreases the risk of microbial attack. Drying must be done quickly, in other words at raised temperatures and with rapid and efficient removal of the water vapor. The most efficient drying is achieved in large driers of the tunnel type. The plant material is spread out on shallow trays, which are placed on mobile racks and passed into a tunnel where they meet a stream of warm air. The air temperature is kept at 20–40 °C for thin materials such as leaves, but is often raised to 60–70 °C for plant parts that are harder to dry, e.g., roots and barks. When the crude drug has been collected under primitive conditions, without access to a drier, it must be dried in the open. Even then, the material should be spread out in shallow layers with good ventilation to

Table 10.1 Maximum final moisture content (MCf) for various medicinal plant species as prescribed in the European pharmacopoeia

Species	Drug	Drug MCf, %w.b
Althaea officinalis L.	Roots	10
Arnica montana L.	Flowers	10
Calendula officinalis L.	Flowers	12
Chamomilla recutita [L.] Rauschert	Flowers	12
Coriandrum sativum L.	Seed	10
Foeniculum vulgare Mill.	Seed	8
Hypericum perforatum L.	Herb	10
Levisticum officinale Koch	Leaves	12
Malva sylvestris L.	Leaves, flowers	12
Melissa officinalis L.	Leaves	10
Mentha x *piperita* L.	Leaves	11
Plantago lanceolata L.	Herb	10
Valeriana officinalis L.	Roots	12
Verbascum phlomoides L.	Herb	12

Source: Europäisches Arzneibuch (Ph.Eur. 5.00) (European pharmacopoeia 2005)

facilitate the drying. The choice of sunshine or shade is determined by the sensitivity to light of the constituents. In a dried drug the enzymes are not destroyed but only rendered inactive due to the low water content. As soon as water is added, they become active again. Hence, dried drugs must be protected from moisture during storage. Maximum final moisture content (MCf), % of wb for various medicinal plant species as prescribed in the European pharmacopoeia is shown in Table 10.1.

iii. **Freeze-drying**

Freeze-drying (lyophilization) is a very mild method. Frozen material is placed in an evacuated apparatus which has a cold surface maintained at −60 to −80 °C. Freeze-drying works by freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublimate directly from the solid phase to the gas phase i.e., water vapor from the frozen material then passes rapidly to the cold surface. The method requires a relatively complicated apparatus and is much more expensive than hot-air drying. For this reason, it is not used as a routine method, but it is very important for drying heat-sensitive substances, e.g., antibiotics and proteins. Some people consider that freeze-dried herbs are superior to other types, but the existing research indicates that freeze-drying imperfectly preserves important classes of medicinal compounds (such as volatiles, phenolics, and carotenoids). However, there is insufficient information to conclude that freeze-drying has negative effects on the medicinal qualities of plants (Abascal et al. 2005).

iv. **Stabilization**

Stabilization is a process of stabilizing the active principles of the crude drugs. On long storage, enzymatic reactions will slowly destroy the constituents, because the last traces of water can never be removed. In order to avoid this degradation, the enzymes should be destroyed before drying, a process usually called stabilization. The most common method is being a brief exposure (a few minutes only) of the plant material to ethanol vapor under pressure (0.5 atm.). Stabilization may be of value for the isolation of compounds that are very susceptible to enzymatic degradation. Stability is an essential factor of quality, safety, and efficacy of a drug product.

v. **Fermentation**

Fermentation or enzymatic transformation of the original plant constituents is sometimes desirable. The fresh material is then placed in thick layers, sometimes covered and often exposed to raised temperatures (30–40 °C) and humidity, so as to accelerate the enzymatic processes. This treatment is usually called fermentation as followed in tea factory. The fermented product must, of course, be dried afterward to prevent attack by microorganisms, e.g., molds. Fermentation is mostly used to remove bitter or unpleasant-tasting substances or to promote the formation of aromatic compounds with a pleasant smell or taste. It is mainly applied to drugs used as spices or stimulants, e.g., vanilla, tea, and cacao.

vi. **Storage**

Storage of crude drugs is very important for stability as well as quality maintenance. There are great differences in the stability of crude drugs because of slow enzymatic changes in the constituents. Drugs containing glycosides and esters are usually less stable than those containing alkaloids. Drugs with essential oils deteriorate rather quickly through evaporation, oxidation, and polymerization of the substances constituting the essential oil. Tannins, on the other hand, have an almost unlimited durability. In order to keep crude drugs as long as possible it is essential to store them in a dry condition in carefully closed containers, it is also advisable to exclude light, because—even if it does not affect the active constituents—it almost always causes changes in the appearance of the drug, especially loss of color and it is also necessary to protect the drug against insect attack.

vii. **Grinding**

Grinding of crude drugs is carried out for different purposes. Regardless of whether the crude drug is to be used for isolation of a pure compound or for manufacture of a simple preparation, the first operation that must be performed is grinding of the plant material to a powder of suitable particle size. It is important that the particles are of as uniform a size as possible. Excessive dust can clog percolators and result in a turbid extract which is hard to clarify. Large particles take a longer time for complete extraction than small ones and large differences in particle size thus slow down the extraction process. Several types of machines are available for grinding

crude drugs including (i) hammer mill (a common type for grinding crude drugs), (ii) knife mill (useful for production of low-dust powders of leaves, barks and roots for subsequent percolation or maceration), (iii) tooth mill (used for production of very fine powders), etc.

Grinding produces a certain amount of heat which must be observed when grinding crude drugs containing heat-sensitive compounds. Mills cooled with liquid nitrogen are available for such purposes. Cold grinding is also preferable for crude drugs containing volatile oils.

Following grinding, the material must be shifted to ensure the proper particle size. Sifting can be performed according to two different principles: sieving and blast sifting.

viii. **Sieving**

In sieving, the material is passed through a sieve of suitable mesh size (coarse—2.00 mm to fine—0.18 mm) giving two fractions. The fraction passing the sieve consists of particles with a size smaller than or corresponding to the mesh size. The remaining fraction consists of coarser particles which are returned to the mill for continued grinding. In blast sifting the material to be classified is blown with compressed air into an apparatus which allows the particles to sediment according to their weight. Coarse, heavy particles settle fast whereas small, light particles stay for a long time in the air stream.

ix. **Extraction**

Extracts can be defined as preparations of crude drugs which contain all the constituents which are soluble in the solvent used in making the extract. They may be dry, soft or fluid. In dry extracts, all solvent has been removed. Soft extracts and fluidextracts are prepared with mixtures of water and ethanol as solvent. Tinctures are prepared by extraction of the crude drug with five to ten parts of ethanol of varying concentration, without concentration of the final product. For both extracts and tinctures, the ratio drug/solvent should always be stated.

Several factors influence the extraction process. Plant constituents are usually contained inside the cells. Therefore, the solvent used for extraction must diffuse into the cell to dissolve the desired compounds whereupon the solution must pass the cell wall in the opposite direction and mix with the surrounding liquid. Equilibrium is established between the solute inside the cells and the solvent surrounding the fragmented plant tissues. The speed with which this equilibrium is established depends on temperature, pH, particle size and the movement of the solvent.

The criteria for ideal solvent for a certain pharmacologically active constituent should be highly selective for the compound to be extracted, should have a high capacity for extraction in terms of coefficient of saturation of the compound in the medium, should not react with the extracted compound or with other compounds in the plant material, should have a low price, should be harmless to man and to the environment, should be completely volatile.

Aliphatic alcohols (up to three carbon atoms), or mixtures of the alcohols with water, are the solvents with the greatest extractive power for almost all natural substances of low molecular weight such as alkaloids, saponins, and flavonoids. According to the pharmacopoeias, ethyl alcoholis the solvent of choice for obtaining classic extracts such as tinctures and fluid, soft, and dry extracts. The ethanol is usually mixed with water to induce swelling of the plant particles and to increase the porosity of the cell walls which facilitates the diffusion of extracted substances from inside the cells to the surrounding solvent. For extraction of barks, roots, woody parts, and seeds, the ideal alcohol/water ratio is about 7:3 or 8:2. For leaves or aerial green parts the ratio 1:1 is usually preferred in order to avoid extraction of chlorophyll.

10.2 Methods of Preparation of Herbal Remedies

Herbal remedies, in traditional systems, are prepared in several ways depending on the plant type, therapeutic constituents, way and purpose of application, etc. Part of the art of herbal medicine relies on the method as to how to best prepare an herb in order for the medicinal properties of that plant to be best released. Herbs can be used both internally and externally, although usually, they are more effective healing agents used internally. Infusions (hot teas), decoctions (boiled teas), tinctures (alcohol–water extracts), macerations (cold-soaking), percolation, digestion, inhalation of powdered plants (like snuff), steam inhalation and even aromatherapy and dry preparations are the main internal preparations, while washes, compresses, poultices, salves, and balms are the main external preparations. A general rule of thumb is that infusions are made with leaves and flowers, while decoctions are made with roots, bark, seeds, and berries.

The therapeutic activity of a medicinal plant is closely related to different groups of chemicals such as essential oils, alkaloids, acids, steroids, tannins, saponins, glycosides. Some of these chemicals are soluble in cold or hot solvents such as water, alcohol, or other organic solvents, and therefore, each one of these classes of chemicals may have a preferred effective method of extraction which facilitates getting the chemicals out of the plant and into the herbal remedy that is being prepared. For example, infusion and decoction are preferred for water soluble chemicals (e.g., anti-inflammatory plant steroids to treat arthritis) while tincture for alcohol soluble chemicals (anti-bacterial alkaloids). This may explain why a tea of the plant is used for arthritis while a tincture is traditionally used to treat various bacterial infections.

Internal Preparations

These herbal preparations are made for internal use by swallowing or inhalation.

i. **Infusion**

An infusion is the simplest form of herbal preparation. It is an herbal preparation in liquid form obtained through extraction of chemical compounds or flavors by

suspending the fresh or dry herbal material for a stipulated period of time (for steeping) in a solvent such as hot water (up to boiling). Water is brought just to a boil and then poured over an herb (or combination of herbs) contained in a container; it is covered and allowed 10–15 min or so for steeping. Infusion is distinct from decoction, which involves boiling the herbal material, or percolation, in which the water passes through the material (as in a coffeemaker). Delicate herbs, tender stem, soft parts of plants such as flowers, leaves, and other plant parts are used for this preparation. It can be prepared in the drinking cup (by just pouring the heated water over the herb in the cup) or by dropping the herb into the pot (ceramic, not metal pot) in which water was heated. Stirring is helpful while steeping, especially with cut herbs. Keeping the infusion covered while steeping is generally recommended. The ratio of herb to water can vary depending on the remedy, the plant, and whether cut herb or powdered herb is used. Generally using 1 teaspoonful of powdered herb or 2 teaspoonful of more bulky cut herb in a 6–8 oz cup (one teacup) of water is sufficient. Infusions are best prepared as needed and taken the same day it was prepared and can be taken hot, warm, or cold.

Method

Preparing an infusion is much like that of tea. Take a warm teapot or any other pot (glass, ceramic or stainless steel) and put 1–2 teaspoonful of dry-fresh herb per cup, pour required quantity of hot water (up to boil) inside (56 g or 2 oz of fresh herb or half of the wt. if dry and pour on 600 ml or 1 pint of boiling water), cover and leave it for about 10–15 min for steeping, strain for the removal of herb and drink. It is best to drink medicinal infusions as hot as possible. The dose is one cupful (6–8 oz) usually three times daily for chronic conditions, or hourly for acute conditions. Preparations should not be kept for more than 24 h. The entire day's dosage can be prepared in the morning. The exceptions are the more aromatic plants with active essential oils. These are best prepared in single dosages (by the cupful) as needed and taken immediately (and while still hot/warm).

When used woody parts, such as bark, seeds, nuts, after breaking up by crushing or chopping add 56 g of fresh herb or 28 g if dry to 600 ml of cold water (i.e., two teaspoonful of fresh or one of dry herb to one cup water). Place in a non-aluminum pan, bring to the boil, cover and simmer for 10–15 min. Strain and allow to cool before drink. If the volume decreases during simmering, make up the volume by adding hot water to the original. The usual dose is one cupful three times daily or hourly for acute conditions. Preparations should not be kept for more than 24 h.

Infusion with Honey

It is a more palatable way to take whole herbs. Use finely chopped fresh, or powdered dry herb. Cover with honey, leave to infuse for a few minutes, and then take on a spoon. This method can be used for essential oils, one drop to a teaspoonful of honey.

ii. **Decoction**

A decoction is a liquid extract made by boiling hard fibrous or woody stem, roots, rhizomes, non-aromatic seeds and barks in water for a longer period of time to

soften the harder material and release its active constituents. It involves first mashing or simmering and then boiling in water to extract chemical substances. Unlike infusions (steeping it in hot water), the plant material is boiled, decoctions are boiled because simple infusion is unable to extract the full medicinal properties of the hard herbal material. Therefore, decoctions and infusions produce liquids with differing chemical properties. Root/ rhizome tea from Angelica (*Angelica archangelica*), Ashwagandha (*Withania somnifera*), Astragalus (*Astragalus membranaceus*), Ginger (*Zingiber officinale*), etc., are some examples of decoctions. Although this method of extraction differs from infusion and percolation, the resultant liquids are often functionally similar.

Method To prepare a decoction, select a saucepan (ceramic, enamel or stainless steel but never aluminum) with a snug fitting lid, measure the amount of herb needed (1 teaspoonful powdered herb or 2 teaspoonful of cut herb per 8 oz or 1 cup of water; 56 g of fresh herb or 28 g if dry, to 600 ml of cold water) into the pot and add the proper amount of cold water depending on how many cups of the decoction to be prepared. Turn on the heat to medium high and bring to a roiling boil. Once it reaches boiling point, cover the pot tightly (valuable essential oils escape through loose lid), turn the heat down to medium or medium-low so that the mixture stays at a good simmer for 20 min. After 20 min, remove from heat and cool slightly. For stronger decoctions using larger woody pieces of bark, longer boiling time (up to 2 h or more to break down, soften, and extract the larger pieces) is required but from smaller woody pieces, the decoction is prepared as usual (boiling 20 min), then it is allowed to sit overnight before straining out the herb. If using cut herbs, strain the mixture through a tea strainer into a teacup and drink while still hot. When straining, make sure to press on the cut herb pieces in the strainer to get as much decoction out of the herb pieces as possible. If using powdered herb, allow the powder to settle to the bottom of the pot and then pour off the decoction from the top into a teacup. Standard dosages for decoction are generally one-half to one cup, two or three times daily. The entire day's dosage can be prepared in the morning (2–3 cups at one time).

iii. **Tincture**

A tincture is an alcoholic herbal extract. Alcoholic solvent is used when plant's active chemicals are not very soluble in water or heat and when a larger quantity is prepared for longer storage. Plant material (dry powder or cut) is soaked in alcohol in an appropriate plant: solvent ratio (usually 1:4) in a concealed vessel (dark colored glass bottle or jar with tight fitting lid or cork), left for 2–6 weeks and strained before use. Alcoholic tinctures are made with various ethanol concentrations, 25% being the most common. The percentage of alcohol and water is unique to the herbs and determines its shelf life; higher percentage of alcohol increases the shelf life of the extract. Many properly prepared plant tinctures stored in the dark bottle out of the sunlight can last several years or more without losing potency. To prepare a tincture with a shelf life of at least one year, it is suggested to use a minimum of 40% alcohol (or 80 US proof vodka or rum without adding any water).

Besides ethanol, other solvents used in herbal tincture preparation include vinegar, glycerol, ether and propylene glycol. Some of these preparations cannot be used for internal consumption. Ethanol has the advantage of being an excellent solvent for both acidic and basic (alkaline) constituents. Glycerin is generally a poor solvent while vinegar, being acidic, is a better solvent for obtaining alkaloids but a poor for acidic components. Non-alcoholic glycerites (extract made using glycerin) offer an alternative for preparations for those who avoid alcohol. Tincture of benzoin (alcoholic solution of benzoin resin, a balsamic resin obtained from the bark of several species of trees in the genus *Styrax*, Styracaceae), Cannabis (an alcoholic extract of flowers, leaves, or stems of *Cannabis sativa*), cantharides (from Spanish fly, *Lytta vesicatoria*), castoreum (exudate from the castor sacs of the mature beaver—*Castor canadensis*, *C. fiber*), opium (laudanum) (contains almost all of the opium alkaloids, including morphine and codeine), pennyroyal (*Mentha pulegium*), spirit of camphor (solution of alcohol and camphor, *Cinnamomum camphora*) are some related examples of tincture. It can be used for poisonous bites, inflammation, blood poisoning, burns and more. St. John's Wort can be used as a tincture to produce beneficial results for depression and anxiety.

Method Herbal tinctures are prepared from raw, dry powder or cut (coarse cut 4 mm, medium cut 2.8 mm fine cut 2 mm) herbal materials and soaked in alcohol to extract the active properties from herbs that will not dissolve in water or in the presence of heat. When working with dried plants, use 2 oz of plant material (cut or powder) for every 8 oz (1 cup) of liquid in the ratio 1:4 or the ratio be 1:5 (200 g or 7 oz dry herb per 1 L or 2.2 pints vodka); measure the amount of cut herb by weight and not volume since many cut herbs can be bulky. Put the herb (powder or cut) in a container containing 40% alcohol (ethanol, 80 US proof vodka, rum, etc.) and leave for 2–6 weeks, strain and use. In the Amazon, a sugar-cane alcohol resembling rum and called aguardiente (alcoholic beverages) is often used to prepare plant tinctures and it is 40–50% alcohol (or 80–100 US proofs). A standard 4:1 tincture usually means 1 part herb to 4 parts liquid (1 oz herb to 4 oz of liquid). To prepare approximately 1 cup of tincture place 2 oz of the herb (powder or cut) into your clean glass container. Pour ½ cup (4 oz) of distilled water and ½ cup (4 oz) of 180 proof alcohols into the container (or 1 cup of 80 proof vodka without water). Seal the container and keep at room temperature away from direct sunlight for at least 2 weeks to soak (larger woody cut pieces need 4 weeks) and shake the container (bottle/jar) periodically, at least once daily. At the end of 2 or 4 weeks, strain the tincture through a muslin cloth or fine mesh strainer. Squeeze out the excess liquid from the herb matter. Discard the plant matter and bottle the tincture in a dark glass bottle and seal.

Since this method uses a higher ratio of plant to liquid and helps concentrate the chemicals through the use of alcohol, dosages needed for tinctures are usually much less than infusions and decoctions. Average dosages for tinctures are about 1–2 milliliters (about 30–60 drops) two to three times daily. The tincture can be placed directly in the mouth for immediate absorption, or placed in a small amount of water or juice. Addition of about 1–2 oz of very hot water in the alcoholic dosage

may help to evaporate alcohol in the hot water in a minute, then cool and drink alcohol-free tincture. Store the tincture at room temperature and away from direct sunlight.

iv. **Maceration**

Macerations can be made out of a wide variety of different plant matter. Any plant matter (herbs or spices) suspended in a liquid (oils, alcohol, vinegar, plain water, honey etc.) and left for a long amount of time to imbue its inherent essences into the suspension can be considered maceration. It is the easiest and most basic method of creating herbal remedies. Maceration process involves a slow steeping of plant matter in any type of liquid, usually (but not limited to), oils. Maceration is a type of cold infusion, a slower time-consuming one that generally does not involve the use of heat. During maceration, plant matter is suspended in a liquid and left for few weeks to few months depending on the desired potency or eventual purpose of the maceration. It is good for the extraction of delicate or highly volatile herbal essences. At its most basic, all macerations are literally cold infusions or very subtle heat infusions.

There are several types of macerations, e.g., herb or spice-infused oil macerations, herb or spice-infused vinegar macerations, herb or spice-infused liquor macerations, herb or spice-infused honey macerations, and plain water-infused cold macerations. Some maceration may be used as massage oils or hair oils, while others may be employed as antiseptics or salves to facilitate wound healing. Still, others may be used a medicine (especially tinctures), that are either drunk straight or (more often than not) diluted with water or some other palatable liquid. With regards to oils, vinegars, and waters, the maceration process renders the suspending liquid quite strong, but not quite as potent as tinctures or essential oils, thereby making them perfectly usable sans any dilution (with a few rare exceptions). Still, one must always try them out for possible adverse reactions prior to use.

Method

This method of preparation is certainly the easiest. The fresh or dried plant material is simply covered in cool water and soaked overnight. The herb is strained out and the liquid is taken. Normally this is used for very tender plants and/or fresh plants, or those with delicate chemicals that might be harmed by heating or which might be degraded in strong alcohol. This is also the easiest to adapt to western methods, since tablets or capsules can be used instead. Alternatively, just stir the ground plant powder into juice, water or smoothies and drink. Maceration can be made by mixing any liquid substance with dry plant matter because moisture in the fresh sample oftentimes causes bacteria and other microbes to multiply and therefore fresh herbs and spices not suggested for macerations. To hasten the process, shake the maceration regularly throughout its sitting or infusing phase, or otherwise gently heat (not simmer or boil, mind you, but simply heat). Another method of quickening the maceration process is to place the suspension in a warm sunny place, preferably under direct sunlight during the whole of the sitting phase. Always use perfectly sterilized and thoroughly dry containers to prevent the possibility of

bacterial formation, always cover it tightly to prevent contamination and spillage and store in a cool, dark environment. After some weeks to some months, strain the decoction through a fine mesh sieve topped by doubled or tripled muslin or cheesecloth into dark-hued mason jars for storage.

v. **Percolation**

Percolation differs slightly from maceration. The powdered drug is dampened with the menstruum (it is an old word meaning solvent, and in herbal circles it refers to the substance, usually liquid, used to extract certain properties from herbs, thus making a medicine), left for 4 h then packed into a percolator. Sufficient menstruum/solvent is added to cover the drug and left for 24 h. The liquid is then allowed to very slowly drain from the bottom of the percolator (about twenty drops per minute). More menstruum/solvent is added and the process continued until the volume in the collecting flask reaches about three-quarters of the required volume. The marc is pressed, this liquid added to the flask, more menstruum/solvent added to make the specified volume then the whole liquid is clarified.

Methods

Methods of preparation, quantitative presence of the active drug constituents in the preparation as well as its mode of use are important for a desired therapeutic effect from an herbal preparation. Fresh materials are considered to be the best, but can be dried to ensure a constant supply throughout the year. In case of dry material, half of the quantity of fresh material may serve the purpose. Methods of preparation of herbal remedies depend on the part of the plant, the active ingredient or the mode of administration. In traditional herbal medicine systems, herbal remedies are prepared in several ways. Some of the methods are described below.

vi. **Syrup**

Syrup is a concentrated solution of sugar in water with specific healing properties. A syrup is classic in treating coughs, mucus congestion, bronchial catarrh and sore throats because it may coat the area and keep the herbs in direct contact with the affected area. Syrups are especially helpful for children and those with a sensitive palate. Basil, mint, rosemary, jasmine, and thyme syrups are examples of some of the common herbal syrups.

Method

(i) Syrups may be made by adding about two ounces of herbs to a quart of water and cautiously boiled down to one pint. While the blend is still warm, two ounces of honey and/or glycerin is added to produce the thickened substance. Licorice and wild cherry bark are popular flavors and therapeutic agents in making syrups. Other herbs that are commonly used are anise seed, comfrey, fennel seed and Irish moss.

(ii) Prepare a syrup using 125 g of sugar in 60 ml of water; bring to the boil while stirring to dissolve the sugar. Add one part of an herbal tincture to three parts syrup. The mixture will keep for a long time since the sugar acts as a

preservative. With infusions or decoctions add 325 g (¾ lb) sugar to each 600 ml, heat while stirring until the sugar dissolves and the mixture thickens. Cool and store in the fridge, in sterile dark bottles with cork stoppers (pressure can build if fermentation occurs).

vii. **Inhalation**

An inhalation is the use of steam to administer herbs or their essential oils. Steam inhalation is a method of introducing warm, moist air into the lungs via the nose and throat for therapeutic benefit. Essential oils are often added to provide additional relief. Steam containing suitable herbal essential oil is one of the best methods to ease breathing, congestion, and stuffy nose. Moisture from a hot shower with the door closed or saline nasal spray is just as helpful to ease congestion. The steam may help ease congestion by loosening mucus and making it easier to clear by blowing nose. Adding menthol, eucalyptus, camphor, thyme, pine etc. oils to the water may help clear the passageways in the nose. Steam inhalation is not advised for children because of the risk of scalding. Instead, it might help a child if they sit in a hot, steamy bathroom. Ancient Egyptians recognized the good therapeutic effects of inhalation therapy through the use of public baths. Steam inhalation has since become a simple and effective home remedy for various health issues (respiratory benefits, natural expectorant, headaches and migraines, pore cleansing and rejuvenation). Inhalation methods may be portable using 1–2 oz bottle and over the bowl inhalation.

Method

Pour boiling or very hot water into a bowl and 3 drops of the essential oil or a few tablespoons of herbs of your choice as per the problem (e.g., use rosemary, eucalyptus, peppermint for clearing nasal passages or lavender, clary sage, vanilla, etc., for calming), place your head about 30 cm above the bowl and cover your head with a towel in such a way that the sides are totally closed and you in actual fact form a tent over the bowl. Do not get the face too close to the hot steam or knock over the bowl, keep your eyes shut and breathe slowly and then deeply through your nose for 1–2 min. If you feel that the treatment is getting too much for you, raise the towel so that fresh air is brought into the area and breathe through your mouth a couple of times and then resume the treatment. Discontinue the treatment when you feel discomfort (at any time). Be careful not to let the steam burn your nose. Use of a humidifier may produce the same effect. When steam and essential oils are combined they form a very potent way to help treat some ailments of the upper respiratory tract, nose, and sinuses. This type of treatment should not be used by anybody suffering from asthma. This is effective against the sufferings due to cold, wheezing chest, sinus discomfort etc., but beyond these discomforts, a licensed medical practitioner should be consulted. When using this treatment with children or elderly people make sure that they do not burn themselves by getting too close to the bowl, or that the steaming water is upset and burns result.

List of some conditions with corresponding herbs (or essential oils) is now available. Same or different herbs or their essential oils may be used in the inhalation therapy to ease difficulties such as breathing (cedar wood, eucalyptus, pine); bronchitis (basil, benzoin, cedar wood, clove, eucalyptus, frankincense, pine, sandalwood, rosemary, tea tree oil, thyme); colds (bay, black pepper, clove, ginger, myrrh, orange, pine, rosemary, tea tree oil); coughing (benzoin, black pepper, cardamom, cedarwood, frankincense, peppermint, rosemary, cypress-a conifer); sinus (basil, rosemary, tea tree oil, eucalyptus, lavender, peppermint, marjoram).

viii. **Bolus (large pill)**

A bolus is a suppository used as an internal poultice in the vaginal or rectal areas. A bolus helps draw toxic poisons to the bolus itself or it is the carrier for healing agents. There are two types of bolus: one that dissolves at body temperature and the other acts as a poultice. The poultice type is made with healing herbs to help draw the poisons and toxins and to help break loose cysts, tumors, and cancerous conditions even as far up as the abdominal area as the bolus has a widespread influence, effecting not only the vagina, but also other organs, such as the bowel and the urinary tract. Boluses are inserted into the rectum for treating ailments such as hemorrhoids and into the vagina for treating vaginal infections and irritations.

Method

The bolus may be made by adding powdered herbs to melted or soft cocoa butter until it forms a compressed and thick consistency. For this, mix one teaspoonful of the powdered herb with a small amount of melted cocoa butter (do not allow it to bubble or burn) and stir a little at a time to have a dough like consistency. If the mixture is too thin, add some turmeric powder and if it is too thick, add some olive or sesame oil. Roll out the mass into a long narrow strip between the palms into a pencil-like form and cut 2.54 cm or 1 in.-long pieces, wrap in wax paper and place in the freezer for 2 h to harden and preserve. Bring the bolus to room temperature before use. Insert the bolus into the vagina or into the rectum. The bolus may be inserted into the vagina to treat infections, irritations or fibroid tumors or into the rectum to treat hemorrhoids or cysts. It is best to use the bolus at night while sleeping when the cocoa butter will melt with the body heat, where the herbs will then be released. Take care to protect clothing and bedding from the melting cocoa butter. Deposits of the bolus should be washed away the following morning.

The herbs used in the bolus are usually astringents. This means that they have a constricting or binding effect. They are able to pull the toxins out of the body. Typical herbs used in a bolus would be white oak or bayberry bark; demulcent herbs will soothe the part or soften the skin to the area applied. Demulcent herbs are comfrey or slippery elm, and antibiotic herbs will inhibit the growth of or destroy microorganisms. Antibiotic herbs are garlic, chaparral or golden seal. Some herbs (all powdered) that are good for bolus, varicosities, hemorrhoids, damaged tissue, softening scar tissue, etc. are: *Hypericum perforatum*, *Hamamelis virginiana*, *Plantago major*, *Capsella bursa-pastoris*, etc.

External Preparations

External or topical remedies are best used for localized skin or muscle complaints, although as the skin is capable of absorbing medicinal constituents, they can be useful for more general complaints as well.

i. **Compresses**

A compress is made by soaking a piece of clean cloth (e.g., linen, cotton, or gauze) folded to form a pad or bandage in a decoction, infusion or tincture and applying it to the affected area, as hot as can be tolerated. When the compress has cooled, it can be soaked again in the reheated liquid and reapplied until the condition has been relieved. Compresses can also be applied cold. A compress is a more concentrated application than a wash, but very useful to accelerate healing of the skin. Compresses are commonly used to treat wounds, eczema, rashes, headaches, muscle aches, fungal skin infections, skin irritation, chest congestion or swelling from an injury. A blend of naturally healing herbs such as calendula flower, black walnut leaf, chaparral leaf, comfrey leaf and root, lobelia, marshmallow root, mullein leaf, skullcap, white oak bark, arnica, plantain, calendula, oats, wild bergamot, chamomile, lavender, rue, and wormwood, traditionally employed as a muscle relaxer, astringent, antiseptic, and vulnerary to heal all manner of connective tissue injuries, are useful in compress.

Method

Make a liter of infusion or decoction (depending on the herbs to be used). Use a clean cloth made of natural fiber such as cotton, linen, or hemp. Soak a pad of the cloth in the hot infusion or decoction (2 cups or 500 ml infusion or decoction, 2 tablespoons or 25 ml tincture in 2 cups or 500 ml water). Wring out the excess liquid and place on the affected area. Before applying, rub a little oil on the affected area to prevent sticking. The heat is an important part of this remedy, so either changes the compress as it cools, or place a hot water bottle on top of the cloth to keep it warm.

Application of hot herbal compresses to restore warmth relieves the pain associated with the initial stage of an injury. Muscles relax, energy and fluid circulation are stimulated (which will normalize inflammation naturally), soothes inflamed membranes, disinfects, draws torn parts together, and proliferates regenerative cell growth. Hot herbal compresses are indicated for sprains, tendonitis, carpal tunnel syndrome, arthritis, bruising, muscle, tendon, ligament, bone, and other connective tissue hurts.

ii. **Poultice**

A poultice is similar to a compress, except that plant parts are used rather than liquid extraction. Poultices are simply moisten herbs applied externally and are commonly used to treat swelling, pain and congestion or be warm crushed fresh or ground powdered herbs that have been applied directly to the skin to relieve abscesses, blood poisoning, bites and eruptions, boils, decrease tissue swelling

(inflammation) and tension, deodorize and disinfect pollutants, soften crusted lesions, encourage the muscles to relax, stimulate healthy skin, and to promote the purging of toxins and healing of the affected area. A poultice may be a hot or moist mass of oil between two pieces of muslin or gauze containing herbs which are applied to the skin to relieve congestion or pain. It may stimulate the absorption of inflammatory toxins produced by the body and to act as a counter-irritant. Antiseptic should be used before applying poultices. Many herbal remedies are applied directly to the skin as poultices—usually on rashes and wounds and as topical pain-relieving remedies. Poultices are prepared in various ways, e.g., from the jungle shaman chewing up fresh leaves or roots and spitting them out onto the skin to mashing up fresh leaves or roots by hand or with a mortar and pestle. Sometimes just enough hot water is poured over dried or fresh plant material to soften them. Then, the wet herbs are placed directly on the skin or between two pieces of cloth and laid on the skin. A light cotton bandage to bind the poultice to the area is generally used or in the outdoor jungle, a nice large flexible leaf is commonly employed and tied with a bit of twine. A poultice is similar to a compress, except that it uses the whole plant matter and not just the liquid extract. Poultices are commonly used for bruises, sprains, inflamed organs, skin complaints and for drawing pus out of infected wounds.

Method

Mash or crush fresh plant parts. Heat them in a pot over boiling water or mix them with a diminutive amount of boiling water. Apply the pulp directly to the skin, as hot as can be tolerated, holding it in place with a gauze bandage. When using dried herb, first powder it and make a paste with 1 tablespoon of powdered herb and a little boiling water or hot organic cider vinegar. The poultice should be a minimum of ¼–½ in. thick. Before applying a poultice, the skin is first covered with oil. It may be held in place with either tape or an elastic bandage and left on for at least 3 h. If the paste is likely to irritate the skin, apply it between two layers of cloth. Poultices can also be left on the body overnight for deep cleansing. Most poultices are applied warm and should not be reheated and then reapplied as toxins have already been absorbed into the poultice pack. When one poultice cools, another may be applied at that time. Use the bruised fresh herbs or powdered dried herbs, which have been mixed to a mush with hot water. It is useful to mix the herb matter with fresh *Aloe vera* gel or castor oil, as this draws the active parts of the plants deep into the skin and underlying tissues. Apply the mix to the affected area and cover with an oiled cloth or plastic wrap to keep the moisture in. Keep it warm with a hot water bottle. Many herbs have a natural drawing power on infections, toxins and foreign bodies embedded in the skin tissue. Plantain and marshmallow are excellent for relieving pain and muscle spasms. Powdered herbs may be moistened with apple cider vinegar, herbal teas, hot water, liniments, or tinctures. A plaster may also be used as a poultice. A potent plaster for drawing out fever may be made by squeezing out water from tofu and mashing the tofu with pastry flour and a large pinch of fresh ginger root.

iii. **Cabbage poultice**

Cabbage poultice improves lymph drainage and helpful in removing toxins.

Method
Finely chop green cabbage sufficient for the area to be treated. Place the cabbage in a blender with just enough water to make a thick paste. Spread the cabbage paste 1 in. thick over a piece of cheesecloth, muslin or a clean tea towel. The size should be sufficient to cover the preferred part of the body. Place the cloth, cabbage-side onto the skin, over the area to be treated. Cover with a clean, dry cloth and wrap the whole area in a thick towel or wool flannel cloth. Leave the poultice in place for 15–60 min depending on the rigorousness of the condition and the reactions of the person. The treated area should get red and warm, but should not get burned. If the person becomes uncomfortable, remove the poultice and wash the area with cool water. Have the person lie down and rest for the duration of the application. After removing the poultice, wash the area with lukewarm water. The cabbage poultice may be repeated two or three times daily as needed, using fresh cabbage each time.

iv. **Compound poultice or plaster**

These are very much like poultices except that the plant materials used are dried and possibly powdered herbs mixed with a carrier or medium such as oatmeal, ground flaxseed, clay, or flour to create a paste when mixed with hot water (e.g., mustard plaster). The hot paste is spread on a piece of cloth and then applied to the affected area. This is covered with another piece of cloth and possibly bound in place by wrapping the area with long strips of cloth. Besides holding the plaster in place for obvious reasons, this also holds in the heat for a bit longer. It may also make this method a little less messy.

v. **Fomentation**

Fomentation (from the Latin word fovimentum means a warm application, to foment means to warm or heat up) is a quaint old term for the application of hot packs or the substance so applied.

Fomentations are used often in natural healing. A fomentation is a special preparation that allows herbs to be absorbed through the skin. A fomentation may be used to treat swellings, pain, colds, and flu.

Method
Prepared first a strong infusion, or tea, from the herb parts (usually the leaves, roots, or flowers), soak a soft white towel or clean cloth in the hot infusion or tea. Leave the towel or cloth wet but not dripping. Apply the fomentation to the affected area as hot as the patient can tolerate. To hold in the heat, cover the soaked towel with warm piece of flannel, or another towel or a few cloth diapers around (because they are thick and absorbent). When it cools, the cloth must be wrung out and dipped again to keep it warm. Fomentation should be applied for several hours at a time and perhaps for several days, depending on the condition being treated. Fomentations stimulate circulation, aid in decongestion, draw abscesses, and are

soothing to external tissue and warm stiff joints. They can be used for acute inflammations, local pains and congestion, neuralgia, toothache, and pleurisy. This fomentation works well for major pain but can also help with more common muscle spasms as well. Cramp bark (*Viburnum opulus*) is fabulous for stopping cramps. It works well for muscle cramps, like when you throw out your back, menstrual cramps or even restless legs. Ginger and cayenne fomentations stimulate circulation and reduce inflammation. Mullein and lobelia fomentations relieve mastitis, thyroid malfunction etc.

vi. **Baths and bathing remedies**

Herbal bath is an age old system of hydrotherapy. In China (1100-221 BC), people used Eupatorium in baths to get rid of body odor. This fragrant herb is a common ingredient to relieve summer heat symptoms and to promote appetite. Here, medicinal plants are added to bath water and the patient is soaked in it. It is also known as vapor bath. This method is like some of the currently evolving dermal delivery systems for drug absorption employed in conventional medicine. The skin is a wonderful organ capable of absorbing plant chemicals (and even synthetic chemicals) directly thru the skin, and into the underlying fat tissue, then into the bloodstream. Since fresh plants are generally used for bathing remedies (chopped or crushed first before adding to the bath water), western adaptations are not always possible when only dried plant materials are available here. In the alternative, try 20–30 oz of a strong decoction or infusion added to your bath water and soak in it for at least 10 min. Bathing with all natural botanical products can be a transformative and nourishing experience. Not just for cleansing, bathing in herbal scented water can help reduce stress, soothe the skin and just be a relaxing experience for everyone. The following list of herbs, such as chamomile, basil, eucalyptus, fennel, lavender, lemon balm, rosemary, sage, calendula, yarrow, can be chosen for their therapeutic offerings such as softening, soothing muscles, stimulating circulation, or drawing out infection. In the summer you can treat yourself to fresh lemon balm leaves or calendula flowers from the garden. Relaxing in a steamy, warm herbal baths is my favorite way to get full body skin care. A good bath herb should be tonic to the skin and relaxing/and or stimulating to the mind. Aromatic herbs that contain essential oils fit the bill perfectly.

The purest natural herbs in the form of highly concentrated essential oils interact with the natural healing and soothing powers of water. Essential oils, known as the immune system of the plant, are inhaled from the steam in your bath and absorbed when you soak in your tub. Water has a natural therapeutic effect on the body's systems. The term hydrotherapy has been used to describe the use of water, hot and cold, to provide a profound therapeutic effect. Adding just a cap of Herbal Bath proves to be a transforming and deeply relaxing, bathing experience. The benefits of warm baths have been known since ancient times. Steam baths are the oldest form of relaxation therapies; they promote blood circulation, open air ways, enhance sweating and mucosal secretions and regulate the immune modulating effect. Heat and moisture promote bodily functions, lubricate the body and regulate the internal water metabolism.

Method

Mix an infusion or decoction to fill the bath or use a large gauze bag stuffed with proper herbs (ground) to steep. When taking herbal bath, the water temperature should be between 37 and 42 °C, rub the body surface slightly and soak in the bath no longer than 30 min. After the bath, rinse the body with plain water, rest for half an hour and drink water to replenish lost body liquid. When adding the essential oils to the hot bath, wait until the water has stopped running to avoid evaporation. Dilute the oils in a base oil or honey, or add at a rate of 10–14 drops per bath as a general rule. In case of using fresh herbs, put them in a muslin bag to steep. To soften skin and remove impurities, dissolve 1 cup of Epsom salts ($MgSO_4$) in the bath water. Bath salts (3 parts Epsom salt to 2 parts baking soda equal or 2 cups total or 1½ cup Epsom salt and ½ cup baking soda) base and essential oils (up to 10 drops of essential oil to every 2 cups of your salt) make an everyday bath into a sweet and sensual, delightful hydrotherapy session.

vii. **Ointment**

An ointment is a therapeutic, fatty, soft substance for external application only. It typically has antiseptic, cosmetic or healing properties. Its usual base is petroleum jelly or lanolin to which the herbal preparation is added. Either form is not water soluble; however, some ointments are composed of ingredients which are water soluble. Ointments are preferably used on the skin when the active principles of herbs are needed for longer periods of time which would then accelerate the healing process. This may be in the case of abrasion, contusion, effusion, or injury. Ointments are preferably used on the skin when the active principles of herbs are needed for longer periods of time which would then accelerate the healing process. This may be in the case of abrasion, contusion, effusion, or injury. Lanolin is a purified, fatlike substance that is natural and obtained from the wool of sheep which may be used instead of petroleum products.

Method

(i) To make an ointment, one or two heaping teaspoons of an herb or herbal preparation is brought to boil in the product of choice (petroleum jelly or lanolin). The mixture is then stirred and strained. When the mixture cools, the ointment is put into jars and is ready to use when the time is right.

(ii) It is made with hot or cold infused herbal oil and beeswax. Using a bain-marie (a piece of cooking equipment, a type of heated bath, water bath), melt about 1 cm square (½ in.) of beeswax in 105 ml (3½ lf oz) of the oil while stirring. Pour into an ointment jar while warm and leave to set. This will keep for about a year.

viii. **Liniment (liquid ointment)**

A liniment is usually comprised of herb and a solvent such as alcohol, vinegar, or oil. It is an herbal extraction that is rubbed into the skin. Liniments are used for sore muscles, strains, arthritis, and inflammations of muscles, ligaments and tendons.

Method

To make a liniment for sore muscles, for example, place 4 oz peppermint in a 16-oz jar. Add 4 oz eucalyptus. Add a pint of alcohol or vinegar. Do not use rubbing alcohol; use vodka. Put in a dry place for 14 days and shake twice a day. Use on the affected areas. A few drops of essential oil such as rosemary, peppermint, or eucalyptus may be added. Alternatively, for sore muscles liniment, fill a jar with 1 part arnica flowers (*Arnica montana*) and 1 part fresh St. John's wort flowers (*Hypericum perforatum*). Fill to the top of the jar with brandy, vodka or apple cider vinegar. Allow the mixture to sit for 2–3 weeks, strain and bottle for use. An instant liniment for muscle pain may be made by combining 0.5 cup alcohol with 1 teaspoon peppermint, eucalyptus or rosemary essential oil. First, try using less essential oil and find the amount that works.

ix. **Herbal oil**

Natural herbal oils include ginseng, jojoba oil, walnut seed oil, sage leaf oil, sweet almond oil, carrot seed oil, and much more. To heal dry skin and hair … also for diminishing scars and stretch marks, to prevent premature aging, to correct prior damage to hair or skin, this oil can be used on skin, hair, and body to rejuvenate and moisturize. Herbal oil moisturizes the skin, hydrates dull skin, and diminishes stretch marks and scars.

Method

Apply and gently rub into skin, for hair—squeeze a small amount into palm of your hand and massage into your hair and let it dry. For body massages to stimulate and relax your entire body, massage into stressed areas on body, for the bath, add a few drops to bath water and soak in the bath, after your bath, your skin will be soft and silky.

To make herbal oil, choose an herb. If it is fresh, allow it to wilt in the sun or overnight to release the excess water that can contribute to mold in the oil. Start with a small jar. If recycling an old food jar, scrub it out and sterilize it. Scrubbing and running through a dishwasher will definitely do the trick. Make sure to sterilize the lid so it does not add an odor to the oil. Make sure the herb is dry and the jar is dry. Fill the jars halfway with herb, then cover with oil and continue until an inch or two of oil is on top. Some herbs that are great for herbal oils are *Calendula officinalis*—an anti-inflammatory, antispasmodic that helps heal wounds, useful for bed sores, broken veins, bruises, inflamed gums, varicose veins, Calendula is also effective on rashes and dry, chapped or cracked skin; Comfrey leaf (*Symphytum officinale*) oil is useful for belly massage, promoting elasticity and preventing stretch marks. It can be used on breasts, hips, and thighs. Comfrey leaf oil also can be used as a massage oil for sprains or muscle tears, to strengthen connective tissue in varicose veins and for dry skin and eczema; St. John's Wort (*Hypericum perforatum*). This is my favorite herbal oil. I use it for everything from sunburned skin, sciatica, carpal tunnel pain, sacral pain in labor, back ache, sore necks, varicose veins, hemorrhoids, wounds and bruises; chickweed oil (*Stellaria media*) oil is useful for pruritus and itchy skin, as well as eczema, hemorrhoids, varicose veins, psoriasis and overall skin health.

x. Cream

The cream formulations may be designed by using ethanolic extracts of *Glycyrrhiza glabra*, *Curcuma longa* (roots), seeds of *Psoralea corylifolia*, *Cassia tora*, *Areca catechu*, *Punica granatum*, fruits of *Emblica officinale*, leaves of *Centella asiatica*, dried bark of *Cinnamon zeylanicum* and fresh gel of *Aloe vera* in varied concentrations (0.12–0.9% w/w). The ethanolic extracts of herbs were incorporated in a cream base that may be prepared by a phase inversion emulsification technique. The cream base was prepared by utilizing oil of *Prunus magdalus*, *Sesamum indicum*, honey, cetyl alcohol, stearic acid, polysorbate monoleate, sorbitan monostearate, propylene glycol and glycerin.

Use aqueous cream to incorporate a little of an infusion, decoction or tincture for application two or three times daily or using emulsifying ointment, dried or fresh herbs can be incorporated directly. Melt two tablespoonsful in a bain-marie and add two teaspoonful of the finely chopped herb, stirring until it takes on the color of the herb. Strain while molten, leave to cool and store in a jar. It remains viable up to a year.

xi. Salves or balms

A salve is a medical ointment (astringent) used to soothe the surface of the body. Salves are useful preparations for regular application, as they are in the form of a cream. Ichthyol salve has been traditionally used to treat minor skin problems such as sebaceous cysts, boils, ingrown toenails, and splinters. The main ingredients are often ichthammol (from sulfur-rich sedimentary rock oil shale or kerogen shale), phenyl alcohol, or *Arnica montana*, and may contain herbs such as Echinacea (coneflowers of Asteraceae) or calendula (pot marigold or marigold of Asteraceae). Common herbs that are prepared as salves are camphor and peppermint for aching muscles, calendula for wound healing and fungal infections, and comfrey or arnica for bruises and broken bones. In herbal salves, the healing powers of medicinal herbs are infused into emollient organic oils and blended with organic beeswax. Within minutes, nourishing oils penetrate and bring the healing and soothing properties of the herbs deep into the tissues. Salves are used externally for minor skin irritations, insect bites, cuts, abrasions, sore muscles, chest congestion and stress relief.

Method

Salves are more complicated to make and are best bought. A simple salve is a firm beeswax and oil combination that is intended for external application. Use olive oil or infused oil such as plantain, comfrey, or calendula. For one pint of oil use about 1–1/2 oz of beeswax or for one ounce of oil use about 1/2 teaspoon of beeswax (an ounce of beeswax is equivalent to about five teaspoons). Heat the oil with the beeswax and mix until all of the wax is melted. Then, add herbs and essential oils and pour into containers. If the salve is too hard, re-melt and add more oil; if too soft, re-melt and add more wax (vegetarian wax or coconut oil may be used instead of beeswax).

xii. **Oil**

Oil is a greasy liquid not miscible with water, usually obtained from and classified as mineral, vegetable or animal. According to character, oils are subdivided as fixed or fatty and volatile or essential. Fixed oils of plants and animals are glyceryl esters of fatty acids. These oils serve as food reserves in animals. They are nonvolatile and contain no acid, e.g., castor oil, olive oil, or cold liver oil. Volatile oils have an odor and produce taste sensations which are obtained from certain plants by steam distillation. These oils are used in flavors, perfumes and healing remedies. They are usually complex chemicals that are difficult to purify (e.g., peppermint or rose). Herb oils are useful when ointments or compresses are not practical. It is important that herb oils be stored in brown glass containers.

Method

When the main property of an herb is much the same as its essential oils, an oil extract may be the best way of preparing a concentrate from fresh herbs. Oils are prepared by softening and pounding the fresh, dried herbs. The oil of choice is then added, approximately 2 oz of an herb to one pint of oil. The mixture is then put in a warm place around 4 days. A swifter process is to carefully heat the oil and herbs in a pan for about 1 h. The oil is then strained and bottled. A small amount of vitamin E may be added as a preservative. Oils are typically made from the aromatic herbs such as eucalyptus, lavender, ginger, peppermint, and spearmint.

Dry Preparations

Herbal preparations often require the use of dried herbs. Herbs are tied to a straight rope or other support upside down or spread on paper towel in an open shelf in a hot dry well ventilated place until they are crisp for grinding.

i. **Powder**

A powder is a collection of fine particles of one or more substances that may be passed through fine meshes. Herbal powders are finely milled herbal material such as dry leaves, flowers, roots, barks, and berries. Powder provides the nutritional and healing benefits of herbs. Powdering herbs is a three step process—drying, grinding and sifting. Freeze-drying or slow-drying at low temperatures preserves phyto-chemical profile of the herbs. Grinding-breaking and sifting—removal of lumps or large particles can be done manually using stone or ceramic grinder and a sieve as well as mechanically. An electrical grinding machine witted with a sieve can be used to facilitate the powdering and sifting of large quantities of herbs into different meshes (coarse—between 20 and 50 mesh to fine—between 60 and 100 mesh). By forming a powder, the herb can be taken either by capsule, in water, in herbal teas, or sprinkled onto food. For external use, the powdered herbs, are used with oil, a petroleum jelly, lanolin, water or even *Aloe vera* juice and applied to the skin to treat abrasions, contusions, effusions, inflammatory processes, and wounds. Powders are used to make herbal capsules, in body powders, tooth powders, and for making spices for cooking and baking recipes. This may seem like a lot of work considering that most herbs and spices are widely available for sale already finely

powdered. The problem is powdered herbs lose their potency, flavor, and aroma very quickly—even when properly stored. The quality of freshly powdered herbs makes it is well worth the effort. Powders may be ingested directly (swallowed with some water or tea) or made into a tea by briefly boiling in hot water, and straining out the dregs that sink to the bottom. Powders may be rolled into sticky pills, called honey boluses, or sliced to make tablets. Powders from agnus to castus berry (chasteberry), Agrimony herb, Alfalfa leaf, Angelica root, Aniseed, Artichoke leaf Astragalus root, Barberry bark, Bogbean leaf, Borage herb Buchu leaf are some of the common examples.

Method
Take necessary fresh plant material such as leaves, flowers, roots, barks, and other useful parts or whole herbs, dry the plant parts as per requirement (freeze-drying or slow-drying at low temperatures preserves phytochemical profile), mash in an electrical grinding machine fitted to a sieve to facilitate the powdering and then sifting into desired meshes (coarse—between 20 and 50 mesh or fine—between 60 and 100 mesh).

ii. **Capsule**

Many herbal medicines are available in capsule or pill form. The herb is ground into a powder and packed in a capsule. This is a convenient method for herbs that are difficult to administer or have an unpleasant taste. Herbs such as *Coptis chinensis*, *Scutellaria baicalensis*, *Phellodendron amourense*, *Gardenia jasminoides*, *Radix Glycyrrhizae*, and *Atractylodes japonica* are bitter tasting but have beneficial medicinal properties. These, among many more herbal medicines, are available in capsules or tablets as it is a much more palatable form. Capsules have the advantage of being easy and convenient, especially for bitter-tasting herbs. The disadvantage of capsules is that the herbs inside them are much harder to assimilate into the body than preparations made with hot water or alcohol.

Method
To take herbs as capsules, you must first buy empty vege-caps, and fill them with the herb. To do this, cover a plate with the powdered herb and take the halves of the capsule apart. Move the halves of the capsule toward each other through the herb powder, filling them in the process. Push the halves of the capsules together to close. Generally speaking, 4 caps need to be taken together to equal 1 teaspoon of herb matter.

10.3 Evaluation, Quality Control and Standardization of Herbal Drugs

Factors that influence the quality of herbal drugs may be enumerated as (i) herbal drugs are usually mixtures of many constituents; (ii) the active principle(s) is (are), in most cases unknown; (iii) selective analytical methods or reference compounds

may not be available commercially; (iv) plant materials are chemically and naturally variable; (v) the source and quality of the raw material are variable; and (vi) the methods of harvesting, drying, storage, transportation, and processing (e.g., mode of extraction and polarity of the extracting solvent, instability of constituents) have an effect.

For standard herbal drug production at industrial level, source herbal ingredients should be analyzed in detail in respect of quality, efficacy, performance, and safety because drugs in commerce are frequently adulterated and do not comply with the standards prescribed for authentic drug. World Health Organization (WHO 2002) puts emphasis on the research and evaluation traditional medicine considering its application since antiquity, popularity and extensive use during the last few decades (owing to natural origin and lesser side effects) as well on the development of appropriate research methodology for evaluating traditional medicine's quality, safety, efficacy, etc.

Quality control for efficacy and safety of herbal drugs and cosmetics is of paramount importance. Quality can be defined as the status of a drug that is determined by identity, purity, content, and other chemical, physical, or biological properties, or by the manufacturing processes. Quality control is a term that refers to processes involved in maintaining the quality and validity of a manufactured product. In general, all preparations, medicines or cosmetics of plant origin, should fulfill the basic requirements of being efficacious and safe, and this can be achieved by suitable practical trials.

Quality control is based on three important pharmacopoeial definitions such as (a) identity (botanical identity); (b) purity: (contaminants free); and (c) content or assay (presence of active constituents at optimum level). For a quality herbal drug production, (i) proper botanical identification; (ii) phytochemical screening; and (iii) standardization are suggested essential steps to be followed strictly.

To prove identity and purity, criteria such as source, type of preparation, physical constants, adulteration, contaminants, moisture, ash content, and solvent residues have to be checked. In most herbal drugs the active constituents are unknown and so the assessment of content is difficult. However, markers can be used for control purposes, but the marker may be independent of any therapeutic activity.

(a) **Identity**: It can be achieved by macro- and microscopical examinations. Voucher specimens are reliable reference sources. Outbreaks of diseases among plants may result in changes to the physical appearance of the plant and lead to incorrect identification. At times an incorrect botanical quality with respect to the labeling can be a problem. For example, in the 1990s, a South American product labeled as 'Paraguay Tea' was associated with an outbreak of anti-cholinergic poisoning in New York. Subsequent chemical analysis revealed the presence of a class of constituents that was different from the metabolites normally found in the plant from which Paraguay tea is made.

(b) **Purity**: It is closely linked with the safe use of drugs and deals with factors such as ash values, contaminants (e.g., foreign matter in the form of other

herbs), and heavy metals. However, due to the application of improved analytical methods, modern purity evaluation also includes microbial contamination, aflatoxins, radioactivity, and pesticide residues. Analytical methods such as photometric analysis, thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), gas chromatography (GC) combined with mass spectrometry (MS), and nuclear magnetic resonance (NMR) can be employed in order to establish the constant composition of herbal preparations. By means of these methods also new insights into the variety of secondary plant metabolites may be obtained.

(c) **Content or assay**: It is the most difficult area of quality control to perform, since in most herbal drugs the active constituents are not known. Sometimes markers can be used. In all other cases, where no active constituent or marker can be defined for the herbal drug, the percentage extractable matter with a solvent may be used as a form of assay, an approach often seen in pharmacopeias. The choice of the extracting solvent depends on the nature of the compounds involved and might be deduced from the traditional uses. For example, when a herbal drug is used to make a tea, the hot water extractable matter, expressed as milligrams per gram of air-dried material, may serve this purpose. A special form of assay is the determination of essential oils by steam distillation. When the active constituents (e.g., sennosides in Senna) or markers (e.g., alkylamides in Echinacea) are known, a vast array of modern chemical analytical methods such as ultraviolet/visible spectroscopy (UV/VIS), TLC, HPLC, GC, MS, or a combination of GC and MS, can be employed.

Botanical extracts made directly from crude plant material show substantial variation in composition, quality, and therapeutic effects. Standardization involves adjusting the herbal drug preparation to a defined content of a constituent or a group of substances with known therapeutic activity by adding excipients or by mixing herbal drugs or herbal drug preparations. Standardized extracts are high-quality extracts containing consistent levels of specified compounds, and they are subjected to rigorous quality controls during all phases of the growing, harvesting, and manufacturing processes. However, no regulatory definition exists for standardization of dietary supplements. As a result, the term ‘standardization’ may mean many different things. Some manufacturers use the term standardization incorrectly to refer to uniform manufacturing practices; following a recipe is not sufficient for a product to be called standardized. Therefore, the presence of the word ‘standardized’ on a supplement label does not necessarily indicate product quality. When the active principles are unknown, marker substance(s) should be established for analytical purposes and standardization. Marker substances are chemically defined constituents of an herbal drug that is important for the quality of the finished product. Ideally, the chemical markers chosen would also be the compounds that are responsible for the botanical’s effects in the body.

There are two types of standardization. (i) True standardization indicates that a definite phytochemical or group of constituents is known to have activity, e.g., Ginkgo products containing 26% flavones and 6% terpenes. These products are

highly concentrated and no longer represent the whole herb, and are now considered as phytopharmaceuticals. In many cases, they are vastly more effective than the whole herb. (ii) This type of standardization is based on manufacturers guaranteeing the presence of a certain percentage of marker compounds; these are not indicators of therapeutic activity or quality of the herb.

Methods of Evaluation of Crude Drugs
For quality control of herbal drugs and cosmetics, different procedures for examination and evaluation are followed such as:

i. Organoleptic evaluation
ii. Microscopic evaluation
iii. Physical evaluation
iv. Chemical evaluation
v. Analytical evaluation
vi. Biological evaluation

10.3.1 Organoleptic Evaluation

Organoleptic evaluation of drugs refers to the evaluation of a drug by color, odor, size, shape, taste and special features including touch, texture, etc. Since the majority of information on the identity, purity, and quality of the material can be drawn from these observations, they are of primary importance before any further testing can be carried out. For this purpose authentic specimen of the material under study and samples of pharmacopoeial quality should be available to serve as a reference. This evaluation procedure provides the simplest and quickest means to establish the identity and purity and thereby ensures quality of a particular sample. If it is found to be devoid of or significantly different from the specified sensory characters such as color, consistency, odor, it is considered as not fulfilling the requirements. Judgment based on the sensory characteristics such as odor, taste, however, may vary from person to person and time to time based on individual's nature. So the description of these features is very difficult so that often the characteristic such as odor and taste can only be described as 'characteristic' and reference made to the analyst's memory. No preliminary treatment is necessary for evaluating the sample in this manner except the softening and stretching of the wrinkled and contracted leaves and flowers, etc.

10.3.2 Microscopic Evaluation

Microscopic evaluation is indispensable in the initial identification of herbs, as well as in identifying small fragments of crude or powdered herbs, and detection of

foreign matter and adulterants. A primary visual evaluation, which seldom needs more than a simple magnifying lens, can be used to ensure that the plant is of the required species, and that the right part of the plant is being used. At other times, microscopic analysis is needed to determine the correct species and/or that the correct part of the species is present. For instance, pollen morphology may be used in the case of flowers to identify the species, and the presence of certain microscopic structures such as leaf stomata can be used to identify the plant part used. Although this may seem obvious, it is of prime importance, especially when different parts of the same plant are to be used for different treatments. Stinging nettle (*Urtica urens*) is a classic example where the aerial parts are used to treat rheumatism, while the roots are applied for benign prostate hyperplasia.

10.3.3 Physical Evaluation

Physical constants are sometimes taken into consideration to evaluate certain drugs. These include moisture content, specific gravity, optical rotation, refractive index, melting point, viscosity and solubility in different solvents. All these physical properties are useful in identification and detection of constituents present in plant.

10.3.4 Chemical Evaluation

Most of the drugs have definite chemical constituents to which their biological or pharmacological activity is attributed. Qualitative chemical test is used to identify certain drug or to test their purity. The chemical methods of evaluation include isolation, purification, and identification of active constituents. Qualitative chemical tests, such as acid value, saponification value, ester value, are useful in evaluation, e.g., resins (acid value, sulphated ash), balsams (acid value, saponification value and ester values), volatile oils (acetyl and ester values), and gums (methoxy determination and volatile acidity). Preliminary phytochemical screening is a part of chemical evaluation. These qualitative chemical tests are useful in identification of chemical constituents and detection of adulteration.

10.3.5 Analytical Evaluation

In general, quality control is based on three important pharmacopoeias definitions, e.g., identity, purity, content, or assay. Content or assay is the most difficult area of quality control to perform, since in most herbal drugs the active constituents are not known. Sometimes markers can be used. Sometimes markers can be used. In absence of a marker, the percentage extractable matter with a solvent may be used

as a form of assay. The choice of the extracting solvent depends on the nature of the compounds involved and might be deduced from the traditional uses. A special form of assay is the determination of essential oils by steam distillation.

To prove identity and purity, criteria such as type of preparation, sensory properties, physical constants, adulteration, contaminants, moisture, ash content, and solvent residues have to be checked. The correct identity of the crude herbal material, or the botanical quality, is of prime importance in establishing the quality control of herbal drugs. Identity can be achieved by macro- and microscopical examinations. Voucher specimens are reliable reference sources. Purity is closely linked with the safe use of drugs and deals with factors such as ash values, contaminants (e.g., foreign matter in the form of other herbs), and heavy metals. Besides these, modern purity evaluation includes microbial contamination, aflatoxins, radioactivity, and pesticide residues examination. Analytical methods such as spectrophotometric analysis, ultraviolet–visible spectroscopy (UV/VIS), infrared spectroscopy (IR), near infrared spectroscopy (NIR), mass spectrometry (MS), nuclear magnetic resonance spectroscopy (NMR) as well as thin layer chromatography (TLC), high-performance liquid chromatography (HPLC), and gas chromatography (GC) can be employed in order to establish the constant composition of herbal preparations.

10.3.6 Biological Evaluation

Some drugs have specific biological and pharmacological activity which is utilized for their evaluation. Actually, this activity is due to specific type of constituents present in the plant extract. For evaluation, the experiments are carried out on both intact and isolated organs of living animals. With the help of bioassays (testing the drugs on living animals), strength of drug in its preparation can also be evaluated. A few important biological evaluations are antibiotic, antifertility, hypoglycemic and neuropharmacological activities.

Some bacteria such as *Salmonella typhi*, *Staphylococcus aureus,* and *Escherichia coli* are used to determine the antiseptic value (the degree of antiseptic activity, e.g., phenol coefficient of certain drugs). The activity of antibiotics is also determined by using *Klebsiella pneumonia*, *Micrococcus flavus*, *Sarcira lutea*, etc. Living bacteria, yeast and molds are used to evaluate certain vitamins. Microbiological assays by cylinder-plate method (in solid medium) and turbidimetric method (in liquid medium) are used in the evaluation of antibiotic activity.

Antifertility drugs include contraceptives and abortifacients. Contraceptive drugs are used to prevent pregnancy and abortifacient to terminate pregnancy. Female rats are used for antifertility activity (anti-ovulation and anti-implantation) and male rats are used for anti-spermatogenic activity (inhibition of spermatogenesis) and spermicidal activity (sperm motility) due to herbal drugs. Rabbits, rats or mice are used to test hypoglycemic activity of plant extract. Radioimmuno assay (RIA) or Enzyme linked immunosorbate assay (ELISA) is done for the measurement of insulin levels.

Neuropharmacological activity tests of the herbal drugs include their effects on central (CNA) and autonomic nervous system (ANS). CNS acting drugs such as cocaine (*Erythroxylum coca*), morphine (*Papaver somniferum*), and cannabinol (*Cannabis sativa*) are tested using rodents. For testing the herbal drugs for their effects on ANS guinea pig ileum for antispasmodic activity, rabbit jejunum for adrenergic activity, rat phrenic nerve-diaphragm for muscle relaxant activity, frog rectus for skeletal muscles activity.

10.3.7 Determination of Foreign

Determination of foreign matter ensures that the stated herbal drugs are made from the specific part of the plant and are devoid of other parts of the same plant or other plants. They should be entirely free from molds or insects, including excreta and visible contaminant such as sand and stones, poisonous and harmful foreign matter and chemical residues. Animal matters such as insects and invisible microbial contaminants, which can produce toxins, are also among the potential contaminants of herbal medicines. Macroscopic examination can easily be employed to determine the presence of foreign matter, although microscopy is indispensable in certain special cases (e.g., starch deliberately added to 'dilute' the plant material). Furthermore, when foreign matter consists, for example, of a chemical residue, TLC is often needed to detect the contaminants.

10.3.8 Determination of Ash Content

Determination of ash content the plant material is done by burning it and followed by the residual ash is measurement as total and acid-insoluble ash. Total ash is the measure of the total amount of material left after burning and includes ash derived from the part of the plant itself and acid-insoluble ash. The latter is the residue obtained after boiling the total ash with dilute hydrochloric acid and burning the remaining insoluble matter. The second procedure measures the amount of silica present, especially in the form of sand and siliceous earth.

10.3.9 Determination of Heavy Metal Contamination

Determination of heavy metal contamination i.e., contamination by toxic metals, either accidental or intentional, such as mercury, lead, copper, cadmium, and arsenic in herbal remedies, is important. It can be attributed to many causes, including environmental pollution, and can pose clinically relevant dangers for the health of the user and should therefore be limited. A simple, straightforward

determination of heavy metals can be found in many pharmacopeias and is based on color reactions with special reagents such as thioacetamide or diethyldithiocarbamate, and the amount present is estimated by comparison with a standard. Instrumental analyses have to be employed when the metals are present in trace quantities, in admixture, or when the analyses have to be quantitative. The main methods commonly used are atomic absorption spectrophotometry (AAS), inductively coupled plasma (ICP) and neutron activation analysis (NAA).

10.3.10 Determination of Microbial Contaminants and Aflatoxins

Determination of microbial contaminants and aflatoxins is necessary because medicinal plants may be associated with a broad variety of microbial contaminants, represented by bacteria, fungi, and viruses. Inevitably, this microbiological background depends on several environmental factors and exerts an important impact on the overall quality of herbal products and preparations. Herbal drugs normally carry a number of bacteria and molds, often originating in the soil. Poor methods of harvesting, cleaning, drying, handling, and storage may also cause additional contamination, as may be the case with *Escherichia coli* or *Salmonella* spp. While a large range of bacteria and fungi are from naturally occurring microflora, aerobic spore-forming bacteria frequently predominate. Laboratory procedures investigating microbial contaminations are laid down in the well-known pharmacopeias, as well as in the WHO guidelines. In general, a complete procedure consists of determining the total aerobic microbial count, the total fungal count, and the total Enterobacteriaceae count, together with tests for the presence of *Escherichia coli*, *Staphylococcus aureus*, *Shigella*, and *Pseudomonas aeruginosa* and *Salmonella* spp. The European pharmacopoeia also specifies that *E. coli* and *Salmonella* spp. should be absent from herbal preparations. However, it is not always these two pathogenic bacteria that cause clinical problems. For example, a fatal case of listeriosis was caused by contamination of alfalfa tablets with the Gram positive bacillus *Listeria monocytogenes*.

10.4 Guidelines for Assessing Quality of Herbal Drugs with Reference to Contaminants and Residues (WHO 2007)

Potentially hazardous contaminants and residues in herbal medicines may be grouped as chemical contaminant (toxic metals and nonmetals, persistent organic pollutants, radioactive contamination, mycotoxins and endotoxins, solvents occurring as contaminants), biological contaminants (microbiological contaminants,

parasitic contamination), agrochemical residues (pesticide residues, extraneous pesticide residues), residual solvents, etc. (Table 10.2).

a. **Contaminants**

i. **Chemical Contaminants**

Toxic Metals and Nonmetals

Contamination of herbal materials with toxic substances such as arsenic can be attributed to many causes. These include environmental pollution, soil composition, and fertilizers. This contamination of the herbal material leads to contamination of the products during various stages of the manufacturing process. Pesticides containing arsenic and mercury were widely used until a few years ago and they are still being used in some countries. As toxic substances are likely to be present in many foods, due to their abundance in nature, it is important to note that concomitant ingestion of herbal products would add to the total concentration of toxic metals consumed by people.

Persistent Organic Pollutants

Persistent organic pollutants (POPs) include organic chemicals, such as the synthetic aromatic chlorinated hydrocarbons, which are only slightly soluble in water and are persistent or stable in the presence of sunlight, moisture, air, and heat. The use of persistent pesticides, DDT and benzene hexachloride (BHC), in agriculture has been banned for many years in many countries. However, they are still found in the areas where they were previously used and often contaminate medicinal plants growing nearby. The Stockholm Convention on Persistent Organic Pollutants currently includes DDT and 11 other POPs including dioxin (a potent carcinogen), aldrin, chlordane, dieldrin, endrin, heptachlor, mirex, toxaphene, and hexachlorobenzene.

Radioactive Contamination

A certain amount of exposure to ionizing radiation is unavoidable because many sources, including of radionuclides occur naturally in the ground and the atmosphere.

Dangerous contamination may be the consequence of a nuclear accident or may arise from other sources. The WHO, in close collaboration with several other international organizations, has developed guidelines for use in the event of widespread contamination by radionuclides resulting from a major nuclear accident. These guidelines emphasize that the health risks posed by herbal medicines accidentally contaminated by radionuclides depend on the specific radionuclide, level of contamination as well as on the dose and duration of use of the product consumed.

Mycotoxins and Endotoxins

The presence of mycotoxins in plant material can pose both acute and chronic risks to health. Mycotoxins are usually secondary metabolic products which are nonvolatile, have a relatively low molecular weight, and may be secreted onto or into the medicinal plant material. Mycotoxins comprise four main groups, namely

Table 10.2 Classification of major contaminants and residues in herbal medicines

General classification	Group	Subgroup	Specific examples	Possible sources	Stage of production at which detectable[a]
a. Contaminants					
i. Chemical contaminants	Toxic and hazardous materials	Toxic metals and nonmetals	Lead, cadmium, mercury, chromium (arsenic, nitrite)	Polluted soil and water, during cultivation/growth, manufacturing process	1, 2, 3, 4
		Persistent organic pollutants	Dioxin aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, mirex	Polluted air, soil, and water, during cultivation/growth	1, 2, 3, 4
		Radionuclide	Cs-134, Cs-137	Air, soil, water during cultivation/growth	1, 2, 3, 4
		Biological toxins	Mycotoxins	Post-harvest processing, transportation, and storage	2, 3, 4
			Bacterial endotoxins	Post-harvest processing, transportation, and storage	1, 2, 3, 4
ii. Biological contaminants	Microorganisms	Bacteria	*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella* species, *Shigella* species, *Escherichia coli*	Soil, post-harvest processing, transportation, and storage	1, 2, 3, 4
		Fungi	Yeast, molds	Post-harvest processing, transportation, and storage	1, 2, 3, 4
	Animals	Parasites	Protozoa–amoebae, Helminths–nematoda	Soil, excreta; organic farming/cultivation, manufacturing process	1, 3, 4
		Insects	Cockroach and its parts	Post-harvest processing, transportation, and storage	1, 2, 4
		Others	Mouse excreta, earthworms, acarus	Post-harvest processing, transportation, and storage	1, 2, 4

(continued)

Table 10.2 (continued)

General classification	Group	Subgroup	Specific examples	Possible sources	Stage of production at which detectable[a]
iii. Solvents		Organic solvents	Acetone, methanol, ethanol, butanol	Soil and water, during cultivation/growth, manufacturing process	1, 2, 3, 4
b. Residues					
i. Agrochemical residues	Pesticides	Insecticides	Carbamate, chlorinated hydrocarbons, organophosphorus	Air, soil, water, during cultivation/growth, post-harvest processing	1, 2, 3, 4
		Herbicides	2,4-D, 2,4,5-T	Air, soil, water, during cultivation/growth, post-harvest processing	1, 2, 3, 4
		Fungicides	Dithiocarbamate	Air, soil, water, during cultivation/growth	1, 2, 3, 4
	Fumigants	Chemical agents	Ethylene oxide, phosphine, methyl bromide, sulfur dioxide	Post-harvest processing	2, 3, 4
	Disease control agents	Antiviral agents	Thiamethoxam	During cultivation	1, 2, 3, 4
ii. Residual solvents		Organic solvents	Acetone, methanol, ethanol, butanol	Manufacturing process	3, 4

[a]Stage of production at which detectable: *1* medicinal plants, *2* herbal materials, *3* herbal preparations, *4* finished herbal products

aflatoxins, ochratoxins, fumonisins, and tricothecenes, all of which have toxic effects. Aflatoxins have been extensively studied and are classified as Group 1 human carcinogens by the International Agency for Research on Cancer. Mycotoxins produced by species of fungi including *Aspergillus*, *Fusarium,* and *Penicillium* are the most commonly reported.

Endotoxins are found mainly in the outer membranes of certain Gram-negative bacteria and are released only when the cells are disrupted or destroyed. They are complex lipopolysaccharide molecules that elicit an antigenic response, cause altered resistance to bacterial infections and have other serious effects. Thus, tests for their presence on herbal medicines should be performed in dosage forms for parenteral use, in compliance with the requirements of national, regional or international pharmacopoeias.

Residual Solvents Occurring as Contaminants

A range of organic solvents are used for manufacturing herbal medicines and can be detected as residues of such processing in herbal preparations and finished herbal products. They should be controlled through GMP and quality control. Solvents to be avoided such as benzene (class I), solvents with limited toxic potential such as methanol or hexane (class II), and solvents with low toxic potential such as ethanol (class III). Solvents used in industries other than the manufacturing of herbal medicines are often detected as contaminants in water used in irrigation, for drinking, and for industrial purposes, and thus, they find their way into medicinal plants and herbal materials at various stages of growth and processing.

Agrochemical Residues

The main agrochemical residues in herbal medicines are derived from pesticides (insecticides, fungicides, nematicides, herbicides, ascaricides, molluscicides and rodenticides) and fumigants.

Examples of fumigants include ethylene oxide, ethylene chlorohydrin, methyl bromide and sulfur dioxide. Medicinal plant materials may contain pesticide residues, which accumulate as a result of agricultural practices, such as spraying, treatment of soils during cultivation, and administration of fumigants during storage. The chlorinated hydrocarbons and related pesticides (e.g., HCH) and a few organophosphorus pesticides (e.g., carbophenothion) have a long residual action. It is therefore recommended that every country producing medicinal plant materials should have at least one control laboratory capable of performing the determination of pesticides using a suitable method.

b. **Biological Contaminants**

Microbiological Contaminants

Herbs and herbal materials normally carry a large number of bacteria and molds, often originating in soil or derived from manure. While a large range of bacteria and fungi form the naturally occurring microflora of medicinal plants, aerobic spore-forming bacteria frequently predominate. Current practices of harvesting, production, transportation, and storage may cause additional contamination and

microbial growth. Proliferation of microorganisms may result from failure to control the moisture levels of herbal medicines during transportation and storage, as well as from failure to control the temperatures of liquid forms and finished herbal products. The presence of *Escherichia coli*, *Salmonella* spp. and molds may indicate poor quality of production and harvesting practices. Microbial contamination may also occur through handling by personnel who are infected with pathogenic bacteria during harvest/collection, post-harvest processing, and the manufacturing process. In order to ensure appropriate and consistent quality of medicinal plant/herbal substances and their products free from microbiological contaminants, it is necessary to establish good agricultural and collection practice (GACP) for herbal starting materials as well good manufacturing practice (GMP), while processing, packaging, and storage of active pharmaceutical ingredients (APIs) also applies to medicinal plants/herbal substances.

Parasitic Contamination

Parasites such as protozoa and nematode, and their ova, may be introduced during cultivation and may cause zoonosis, especially if uncomposted animal excreta are used. Contamination with parasites may also arise during processing and manufacturing if the personnel carrying out these processes have not taken appropriate personal hygiene measures.

Chromatography and Chemical Fingerprints of Herbal Medicines for the Purpose of Quality Control of Herbal Medicines

By definition, a chromatographic fingerprint of an herbal drug is a chromatographic pattern of the extract of some common pharmacologically active chemical components. This chromatographic profile should be featured by the fundamental attributions of integrity and fuzziness or sameness and differences so as to chemically represent the herbal drug investigated. It is suggested that with the help of chromatographic fingerprints obtained, the authentication and identification of herbal medicines can be accurately conducted (integrity) even if the amount and/or concentration of the chemically characteristic constituents are not exactly the same for different samples of drug (hence, fuzziness) or, the chromatographic fingerprints could demonstrate both the sameness and differences between various samples successfully.

It is very tough to obtain reliable chromatographic fingerprints that represent pharmacologically active and chemically characteristic components because of the presence of innumerable number of unknown components in herbal drug and its extract, low concentration, and variability, even within the same herbal materials. Under these circumstances, chromatographic technique is useful to separate the complex chemical components in herbal extracts into many relatively simple subfractions. Based on the conception of phytoequivalence, the chromatographic fingerprints of herbal medicines could be utilized for addressing the problem of quality control of herbal medicines. Chemical fingerprints obtained by chromatography, especially by hyphenated chromatography, are strongly recommended for the purpose of quality control of herbal medicines, since they might represent

appropriately the chemical integrities of the herbal medicines and therefore be used for authentication and identification of the herbal products.

In general, the methods for quality control of herbal medicines involve sensory inspection (macroscopic and microscopic examinations) and analytical inspection using instrumental techniques such as thin layer chromatography, high-performance liquid chromatography (HPLC), gas chromatography coupled with mass spectrometry (GC–MS), liquid chromatography coupled with mass spectrometry (LC–MS), near infrared (NIR), and spectrophotometer. TLC was the common method of choice for herbal analysis before instrumental chromatography methods such as GC and HPLC were established. TLC is still frequently used for the analysis of herbal medicines since various pharmacopoeias such as Indian herbal pharmacopoeia, Ayurvedic pharmacopoeia; American Herbal Pharmacopoeia (AHP), Chinese drug monographs and analysis, pharmacopoeia of the People's Republic of China. TLC is a technique in which a solute undergoes distribution between two phases, a stationary phase acting through adsorption and a mobile phase in the form of a liquid. The adsorbent is a relatively thin, uniform layer of dry finely powdered material applied to a glass (most commonly used), plastic or metal plate or sheet. Separation may also be achieved on the basis of partition or a combination of partition and adsorption, depending on the particular type of support, its preparation and its use with different solvent. Identification can be effected by observation of spots of identical Rf value and about equal magnitude obtained, respectively, with an unknown and a reference sample chromatographed on the same plate. A visual comparison of the size and intensity of the spots usually serves for semi-quantitative estimation. TLC is an easier method of initial screening with a semi-quantitative evaluation. HPTLC is one of the sophisticated instrumental techniques based on the full capabilities of TLC. It is most flexible, reliable and cost efficient separation technique. The advantage of automation, scanning, full optimization, selective detection principle, minimum sample preparation, hyphenation, and so on enable it to be powerful analytical tool for chromatographic information of complex mixtures of pharmaceuticals, natural products, clinical samples, food stuffs, and so on. The advantages of using TLC and also HPTLC to construct the fingerprints of herbal medicines are its simplicity, versatility, high velocity, specific sensitivity and simple sample preparation. Thus, it is a convenient method of determining the quality and possible adulteration of herbal products.

The analysis of volatile compounds by high sensitive gas chromatography (GC) is very important in the analysis of herbal medicines. The GC of the volatile oil gives a reasonable fingerprint (in respect of composition and relative concentration) which can be used to identify the plant. The extraction of the volatile oil is relatively straightforward in GC and can be standardized and the components can be readily identified using GC–MS analysis.

HPLC is a popular and easy method and can be used to analyze almost all the compounds (both volatile and stable compounds) in the herbal medicines. Reversed-phase (RP) columns may be the most popular columns used in the analytical separation of herbal medicines. The optimal separation condition for the HPLC involves many factors, such as the different compositions of the mobile

phases, their pH adjustment, pump pressures. Thus, a good experimental design for the optimal separation seems in general necessary. In order to obtain better separation, some new techniques have been recently developed in research field of liquid chromatography, e.g., micellar electrokinetic capillary chromatography (MECC), high-speed counter-current chromatography (HSCCC), low-pressure size-exclusion chromatography (SEC), reversed-phase ion-pairing HPLC (RP-IPC-HPLC), and strong anion-exchange HPLC (SAX-HPLC).

The advantages of HPLC lie in its versatility for the analysis of the chemical compounds in herbal medicines. The single wavelength UV-HPLC used for the chromophoric compounds can be replaced by the HPLC coupled with evaporative light scattering detection (HPLC–ELSD) for the analysis of non-chromophoric compounds. This ELSD aided HPLC is useful for the analysis of many pharmacologically active components in herbal medicines and thus quite suitable for the construction of the fingerprints of the herbal medicines, since the response of ELSD depends only on the size, shape, and number of elute particles. For structure elucidation of the chemical components in herbal medicine, it is necessary to use the hyphenated HPLC (e.g., HPLC–MS, HPLC–NMR), i.e., chromatographic separation system on-line with a spectroscopic detector. For most (trace-level) analytical problems in the research field of herbal medicines, the combination of column liquid chromatography or capillary gas chromatography with a UV–VIS or a mass spectrometer or HPLC coupled with diode array detection (HPLC–DAD), capillary electrophoresis coupled with diode array detection (CE-DAD), gas chromatography coupled with mass spectrometry (GC–MS) and liquid chromatography coupled with mass spectrometry (LC–MS) becomes the preferred approach for the analysis of herbal medicines.

10.5 Adulteration of Crude Drugs

Adulteration is a practice of substituting the original crude drug partially or fully with other substances which are either free from or inferior in therapeutic and chemical properties or addition of low grade or spoiled drugs or entirely different drug similar to that of original drug substituted with an intention of enhancement of profits, or adulteration may be defined as mixing or substituting the original drug material with other spurious, inferior, defective, spoiled, useless other parts of same or different plant or harmful substances or drug which do not confirm to the official standards. The adulteration and substitution of herbal drugs are the burning problem in herbal industry and it has caused a major effect in the commercial use of natural products. Adulteration in market samples is one of the greatest drawbacks in promotion of herbal products. The ways through which adulterations happen may be direct or intentional, and indirect or unintentional.

Direct or Intentional Adulteration

Direct or intentional adulteration occurs with bad intention of the manufacturer or supplier for high benefit. Direct or intentional adulteration is done deliberately and includes practices in which an herbal drug is substituted partially or fully with other inferior products. Trader's preference to low quality cheaper herbal products and reluctance to pay high prices for high-quality herbs ultimately encourages producers and traders in intentional adulteration. Following are some of the ways and means of adulteration of commercial herbal products.

(i) **With artificially manufactured materials**: Substances artificially manufactured being resembled with original drug are used as substitutes. This practice is generally followed for much costlier drug e.g., nutmeg is adulterated with basswood prepared to the required shape and size; the colored paraffin wax is used in place of beeswax.

(ii) **With inferior quality materials**: Morphological resemblance alone may not ensure the therapeutic authenticity or value of the adulterant as that of original natural drug e.g., Belladonna (*Atropa belladonna*) leaves are substituted with Ailanthus (*Ailanthus altissima*) leaves, papaya (*Carica papaya*) seeds to adulterate *Piper nigrum*, mother cloves and clove stalks are mixed with clove, beeswax is substituted by Japan wax.

(iii) **With exhausted material**: In this type, the same drug is admixed but devoid of any medicinally active constituents as they are already extracted out. This practice is more common in case of volatile oil containing drugs such as fennel, clove, coriander, caraway. Sometimes natural characters of exhausted drugs such as color and taste are manipulated by adding other additives and then it is substituted, e.g., exhausted gentian made bitter with aloes. Apiaceae fruits and cloves (*Syzygium aromaticum*) after extraction of volatile oils (after exhaustion) are adulterated with exhausted original drugs, exhausted jalap (tuberous roots of *Ipomoea purga*, *I. jalapa*) and Indian hemp (*Cannabis indica*) after exhaustion of resins are used as adulterant.

(iv) **With foreign matter**: Sometimes synthetic chemicals are used to enhance the natural character e.g., addition of benzyl benzoate to balsam of Peru, citral to citrus oils such as oil of lemon and orange oil.

(v) **With harmful or fictitious substances**: Different parts of the same plant without active ingredients, sand, stones, manufactured artifacts, synthetic inferior principles and other foreign matter are used as adulterants. Sometimes the wastes from market are collected and admixed with authentic drugs particularly for liquids or unorganized drugs e.g., pieces of amber colored glass in colophony, limestone in asafetida, lead shot in opium, white oil in coconut oil, cocoa butter with stearin or paraffin.

(vi) **Adulteration of powders**: Besides entire drug powder form frequently found to be adulterated e.g., powder liquorice or gentian admixed with powder olive stones, under the name of cinchona, *Cinchona calisaya*, *C. officinalis*, *C. ledgeriana* and *C. succirubra* are available as mixtures.

Indirect or Unintentional Adulteration

Unintentional or undeliberate adulteration sometimes occurs without bad intention of the manufacturer or supplier. Sometimes in the absence of proper means of evaluation, an authentic drug partially or fully devoid of the active ingredients may enter the market. Factors such as geographical sources, growing conditions, processing, and storage are all factors that influence the quality of the drug. Some are described in the following paragraphs.

(i) **Faulty collection**: Some of the herbal adulteration is due to the carelessness of herbal collectors and suppliers. The correct part and tot the other less valuable part of the genuine plant should be collected. Moreover, collection should be carried out at a proper season and time when the active constituents reach maximum. *Datura strumarium* leaves should be collected during flowering stage and wild cherry bark in autumn etc. Collection from other plant by ignorance, due to similarity in the appearance, color, lack of knowledge may lead to adulteration, e.g., collection of *Aconitum deinorhizum* in place of *Aconitum napellus*, or *Rhamnus californica* in place of *Rhamnus purshiana* (cascara bark) lead to adulteration. Confusion existing in the common vernacular name of different plants or different vernacular names of the same plant in various places of the country may lead to this type of adulteration. Often in different states, the same plant is known by. This creates confusion which is best illustrated by Punarnava (*Boerhavia diffusa*) and Brahmi (*Bacopa monnieri*).

(ii) **Imperfect preparation**: Non-removal of associated or undesirable parts or structures e.g., stems from leaves, flowers, fruits, cork should be removed from ginger rhizome etc. Proper drying conditions should be adhered, e.g., if digitalis leaves are dried above 65 °C, enzymatic hydrolysis may lead to decomposition of glycosides. Excessive heat is used in separating the cod liver oil from livers, where the proportions of vitamins, odor, color, etc., are adversely affected.

(iii) **Incorrect storage**: Deterioration of herbal drugs due to improper storage condition (air, humidity, light, and temperature) may lead to the development of organisms such as molds, mites, and bacteria and loss of the active ingredients, production of metabolites with no activity or with toxic effects. Oxidation of the constituents of a drug can be brought about by oxygen in the air, causing some products, such as essential oils, to resinify or to become rancid. Moisture or humidity and elevated temperatures by accelerating enzymatic activities deteriorate and decompose the herb, e.g., volatile oils should be protected from light and stored in well-closed containers in cool place, Belladonna leaf should be stored in moisture free containers, otherwise enzymatic decomposition of active constituents will happen. Mites, nematode worms, insects, and beetles can also destroy herbal drugs during storage.

(iv) **Gross substitution**: Gross substitution with plant material due to morphological resemblance i.e., similarity in appearance, colors, etc. the genuine crude drugs are substituted with others are very often sold in the market, e.g.,

Podophyllum peltatum is used as a substitute for *P. hexandrum*, Belladonna leaves are substituted with Ailanthus leaves, saffron is admixed with dried flowers of *Carthamus tinctorius*, mother cloves and clove stalks are mixed with clove.

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Chapter 11
Microscopy in Pharmacognosy

Abstract Microscopy is useful for the study of the internal structure, constitution, and inclusions of plant and animal cells or other objects in detail. It is necessary for the detection of adulterants and contaminants of the herbal preparations and thus provides means for assessing the authenticity and quality of herbal drugs. Size, shape, relative position of different cells and tissues as well as the chemical nature of the cell walls, and the form and nature of cell contents are considered during microscopic analysis of crude drugs. Electron microscope uses electron beam to illuminate a specimen and thus has greater resolving power than a light microscope which uses visible light. Depending on the number of eyepieces or ocular lenses, a microscope may be mono-, bi-, and trinocular, and bright-field, dark-field, phase-contrast, florescence microscope, etc., are light microscopes while transmission, scanning, reflection, scanning transmission, low-voltage electron, etc., are electron microscopes. Botanical microscopic atlas uses the characteristics of botanically authenticated multiple samples that have been compared and cross-checked against other microscopic characterizations for consistency and completeness. Microscopic evaluation of botanical drugs may be of both qualitative and quantitative. Qualitative microscopy includes studies of the transverse sections of leaf, root bark, as well as longitudinal section of root bark under photomicrograph with or without staining. In case of powder microscopy, different staining reagents such as iodine for detection of starch grains and calcium oxalate crystals while phloroglucinol for detection of lignified components are used. Quantitative microscopy of some pharmacognostic parameters like vein-islet number, vein termination number, stomatal number, stomatal index, and palisade ratio are used for identification, purity determination, and evaluation of crude leafy drugs. Drawing of morphological and histological structures of plant and animal organs and various other minute structures (e.g., trichomes, glands, stomata, calcium oxalate crystals) is also used for quantitative microanalysis of admixed or adulterated powdered drugs. Plant sections or powders of the drug are mounted in water or dilute glycerol for light microscopic examination. Color and clearing, bleaching and defatting reagents are used to stain and clear prior to microscopic examinations. Tissues are macerated by using chemicals to disintegrate the middle lamella and isolation of tissues for study. The characteristic microscopic features include trichomes,

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palisade and spongy parenchyma, collenchyma, stomatal frequency, their index, vein-islet, vein termination number, palisade ratio, shape and size, as well as vascular bundles, xylem and phloem cells, inclusions, etc., and their physical constants for leafy drugs while cork cambium, primary cortex, phloem fibers, medullary rays, endodermis, pericycle, vascular bundles, etc., in the transverse and longitudinal sections, and their physical constants stand as characteristic microscopic features of drugs from root, stem, etc. Micrometry and camera lucida drawing to scale of tissues, cells, cellular elements, cell inclusions, and other minute structures are of significant value in the examination of crude drugs for quality assessment in presence of adulterants. With the worldwide increase in popularity and acceptance of herbal medicines, the classical tool like microscopy is urgently needed for the assessment and quality control of plant products such as crude herbal drugs, registered herbal medicinal products, over-the-counter herbal products, or health foods. Modern pharmacopoeias offer new monographs on herbal drugs, including their microscopic characterization.

Keywords Microscopy · Light and electron microscope · Botanical microscopic atlas · Micrometry · Camera lucida drawing

Pharmacognosy is an applied science, and it utilizes many techniques and procedures originated and developed by ancillary sciences. Sometimes such techniques have been modified to better meet the peculiar needs of quantitative microscopy (Hampton Hoch 1948). Microscopy (microscopic examination) is an important technique used in pharmacognosy for the study and identification of crude drugs. According to American Herbal Pharmacopoeia, microscopic characterizations of botanical medicines introduce botanical microscopy to the industry as a low-cost quality assessment tool for the physical examination of botanicals and highlight the value of botanical microscopy as an important physical assessment tool for botanicals (Anonymous 1911). Microscopy provides methods for assessing the authenticity and quality of herbal drugs.

Microscope (also magnifying lens) is an optical instrument that magnifies smaller objects and thus helps to study their details—structure, constitution, and inclusions. It is also used to study the details of the internal structure and contents of large objects, plant parts, and animal tissues. Based on light sources for transmission (visible or electronic beam), microscopes are classified into two broad groups: (i) Light microscope, both simple and compound, uses visible light from sun or electric bulb (Figs. 11.1 and 11.2), and (ii) Electron microscope, which uses an electron beam to illuminate a specimen (Fig. 11.3). An electron microscope has greater resolving power than a light microscope and can reveal the structure of smaller objects because electrons have wavelengths about 100,000 times shorter than visible light photons. Light microscope includes bright-field, dark-field, and phase-contrast and florescence microscope while electron microscope may be

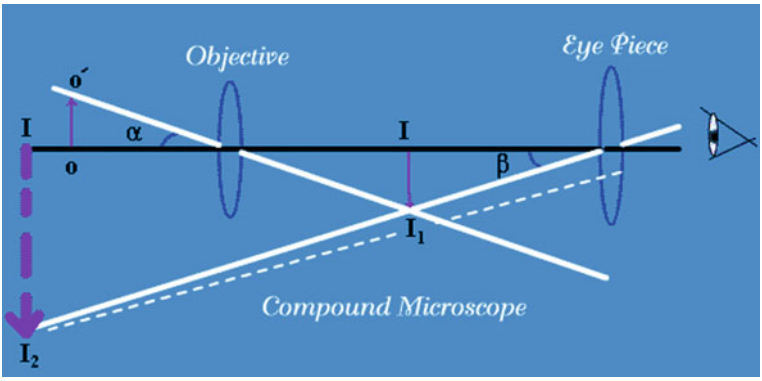

Fig. 11.1 Working principle and magnification of microscope

transmission electron microscope, scanning electron microscope, reflection electron microscope, scanning transmission electron microscope, and low-voltage electron microscope (Fig. 11.3). Microscope may be mono-, bi-, and trinocular depending on the presence of the number of eyepieces or ocular lenses.

11.1 Construction and Working Principles of Compound Microscopes

The simple microscope has limited magnifying (10×) capacity. The compound microscope (common light microscope used in the laboratory) produces high magnification. It is basically made by using two convex lenses of short focal length. They are arranged vertically on a common axis at certain distance from each other. The first of these lenses (lower one), called the objective lens, produces the primary image (I) of the object (O) placed under it. This is an enlarged, real, inverted image of the object. This image then acts as an object for the second lens (upper one), called the ocular or eye lens, which gives a still further enlarged virtual image (I) of the object. This is the image, which is seen by the eye of the observer. Magnification of a specimen is the function of a two-lens system; the ocular lens is found in the eyepiece, and the objective lens is situated in a revolving nosepiece.

Microscope magnification calculation examples: When the ocular lens is 10× and the objective lens is 10×, the field of view is 800 μm. How to calculate the field of view when the ocular lens is 40× and the objective lens is 100×? The magnification at lower power is 10 × 10 = 100. The magnification at higher power is 40 × 100 = 4000, higher power field of view = 100 × 800/4000 = 20 μm.

A compound microscope essentially contains the following components:

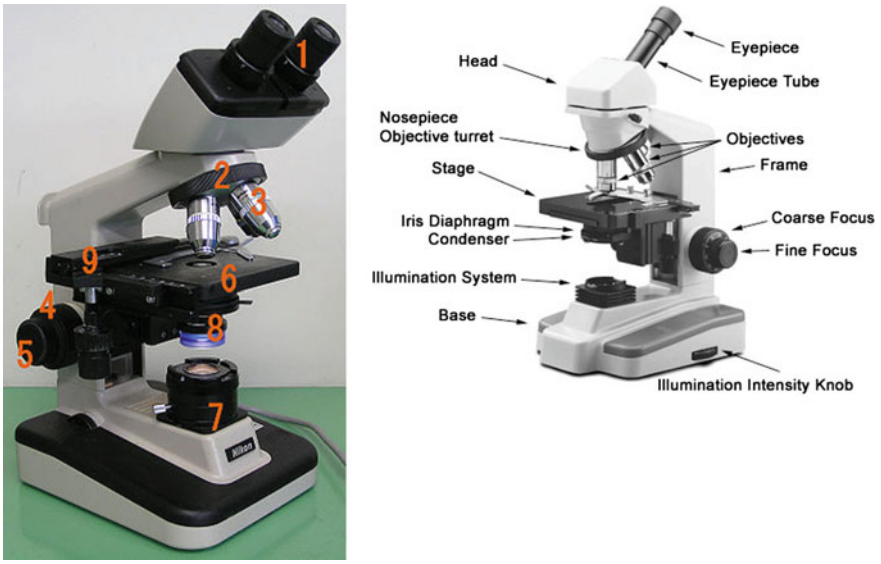

Fig. 11.2 A compound binocular microscope (light). Ocular lens (eyepiece) (*1*), objective turret or revolver or revolving nosepiece (to hold multiple objective lenses) (*2*), objective (*3*), focus wheel to move the stage (*4*—coarse adjustment, *5*—fine adjustment), frame/stage (*6*), light source, a light or a mirror (*7*), diaphragm and condenser lens (*8*), stage and clip (to hold sample) (*9*)

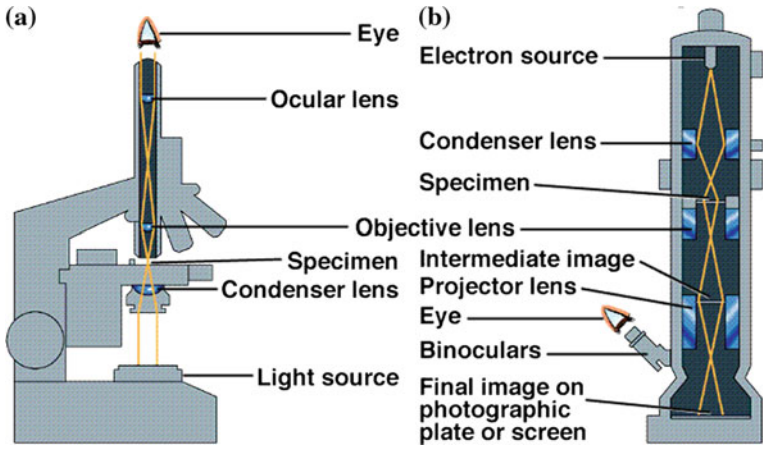

Fig. 11.3 Comparison of **a** compound optical microscope and **b** transmission electron microscope, TEM

A compound microscope essentially consists of the following parts:

(i) **Eyepiece**: The lens closest to the eye is called the eyepiece or ocular. It is the uppermost component part of the microscope through which it holds the eye lens of the microscope.

(ii) **Drawtube**: This is a vertical metallic tube, which houses the eyepiece at its upper end and the nosepiece at the lower end. It moves up and down by two adjustment knobs (coarse and fine).

(iii) **Nosepiece:** This is moveable circular metallic disk fitted at the lower end of the drawtube and holds the objectives.

(iv) **Objective:** The lens closest to the object is called the objective. The objective is a small metallic tube, which holds the objective lens. It screws into the nosepiece.

(v) **Stage:** The stage is a dark colored rectangular or circular metallic support on which the object (mounted on a glass slide) is placed for examination. It is fitted below the nosepiece and is provided with a central hole to allow light to pass through the object. It has two clips to hold the slide with the object in position.

(vi) **Condenser:** It is an optical part on a metallic casing under the stage which condenses light rays to a strong beam to illuminate the object correctly.

(vii) **Diaphragm:** is located on the condenser and controls the amount of light coming through it. Both coarse and fine adjustments are found on the light microscope. The condenser is provided with an adjustable diaphragm, which controls the amount of illuminating light.

(viii) **Light source:** The object is illuminated either by a built-in light source fitted below the condenser, or by an external source of light. In the latter case, the light is reflected to the object by an adjustable plano-concave reflector mirror fitted under the condenser.

(ix) **Stand:** In order to carry the eyepiece, objective, and condenser in strict alignment along the optical axis and to maintain the stage perpendicular to the axis, the microscope is assembled in a strong mechanical frame, called the stand. The stand is provided with a heavy foot, often shapes like a horse shoe, in order to ensure stability of the instrument, and a limb which supports the optical unit, the stage and the adjustable knobs. The limb is attached to the foot by a hinged joint so that the microscope may be set at any desired angle.

Magnification is the ratio of enlargement between the specimen and its image (either printed photograph or the virtual image seen through the eyepiece). To calculate magnification, we multiply the power of each lens through which the light from the specimen passes, indicating that product as GGG×, where GGG is the product. For example, if the light passes through two lenses—an ocular lens 10× and an objective lens 4×, we multiply the 10× ocular value by the value of the objective lens to get the product as $10 \times 4 = 40$, or 40× magnification.

A compound light microscope often contains four objective lenses such as the scanning lens (4×), the low-power lens (10×), the high-power lens (40×), and the oil-immersion lens (100×). With an ocular lens that magnifies 10 times, the total

magnifications possible will be 40× with the scanning lens, 100× with the low-power lens, 400× with the high-power lens, and 1000× with the oil-immersion lens. Most microscopes are parfocal, i.e., the microscope remains in focus when one switches from one objective to the next objective.

Working distance is the distance between the specimen and the magnifying lens. Depth of field is a measure of the amount of a specimen that can be in focus. Magnification and resolution are terms used frequently in the study of cell biology, often without an accurate definition of their meanings. Magnification is a ratio of the enlargement (or reduction) of an image (drawing or photomicrograph), usually expressed as ×1, ×1/2, ×430, ×1000, etc. Resolution is the ability to distinguish between two points. Generally, resolution increases with magnification, although there does come a point of diminishing returns where you increase magnification beyond added resolution gain.

Resolution of a microscope is the ability to see clearly two items as separate objects under the microscope. The resolution is determined in part by the wavelength of the light used for observing. Visible light has a wavelength of about 550 nm, while ultraviolet light has a wavelength of about 400 nm or less. The resolution of a microscope increases as the wavelength decreases, so ultraviolet light allows one to detect objects not seen with visible light. The resolving power of a lens refers to the size of the smallest object that can be seen with that lens. The resolving power is based on the wavelength of the light used and the numerical aperture of the lens. The numerical aperture (NA) refers to the widest cone of light that can enter the lens; the NA is engraved on the side of the objective lens.

If the user is to see objects clearly, sufficient light must enter the objective lens. With modern microscopes, entry to the objective is not a problem for scanning, low-power, and high-power lenses. However, the oil-immersion lens is exceedingly narrow, and most light misses it. Therefore, the object is seen poorly and without resolution. To increase the resolution with the oil-immersion lens, a drop of immersion oil is placed between the lens and the glass slide. Immersion oil has the same light-bending ability (index of refraction) as the glass slide, so it keeps light in a straight line as it passes through the glass slide to the oil and on to the glass of the objective, the oil-immersion lens. With the increased amount of light entering the objective, the resolution of the object increases, and one can observe objects as small as bacteria. Resolution is important in other types of microscopy as well.

In addition to the familiar compound microscope, microbiologists use other types of microscopes for specific purposes. These microscopes permit viewing of objects not otherwise seen with the light microscope. (i) An alternative microscope is the dark-field microscope, which is used to observe live spirochetes, such as those that cause syphilis. This microscope contains a special condenser that scatters light and causes it to reflect off the specimen at an angle. A light object is seen on a dark background. (ii) A second alternative microscope is the phase-contrast microscope. This microscope also contains special condensers that throw light ‘out of phase’ and cause it to pass through the object at different speeds. Live, unstained organisms are seen clearly with this microscope, and internal cell parts such as mitochondria, lysosomes, and the Golgi body can be seen with this instrument.

The fluorescent microscope uses ultraviolet light as its light source. When ultraviolet light hits an object, it excites the electrons of the object, and they give off light in various shades of color. Since ultraviolet light is used, the resolution of the object increases. A laboratory technique called the fluorescent-antibody technique employs fluorescent dyes and antibodies to help identify unknown bacteria.

Electron microscopes work in similar way as normal optical microscopes. Electron microscope uses beam of accelerated electrons (up to 100,000 times shorter than that of visible light photons) as a source of illumination while light microscope uses visible light spectrum for this purpose. Because of this fact, the electron microscope has a higher resolving power than a light microscope and can reveal the structure of nano-objects and even an atom. A transmission electron microscope (TEM) can achieve better than 0.5 Å or 50 pm resolution and magnifications of up to about 10,000,000× whereas most light microscopes are limited by diffraction to about 200 nm resolution and useful magnifications below 2000×.

The transmission electron microscope uses electrostatic and electromagnetic lenses to control the electron beam and focus it to form an image. These electron optical lenses are analogous to the glass lenses of an optical light microscope.

The electron microscope uses electrostatic and electromagnetic 'lenses' to control the electron beam and focus it to form an image. These lenses are analogous to, but different from the glass lenses of an optical microscope that forms a magnified image by focusing light on or through the specimen. Electron microscopes are used to observe a wide range of biological and inorganic specimens including microorganisms, cells, large molecules, biopsy samples, metals, and crystals. Industrially, the electron microscope is often used for quality control and failure analysis. Since the beam of electrons has an exceptionally short wavelength, it strikes most objects in its path and increases the resolution of the microscope significantly. Viruses and some large molecules can be seen with this instrument. The electrons travel in a vacuum to avoid contact with deflecting air molecules, and magnets focus the beam on the object to be viewed. An image is created on a monitor and viewed by the technologist.

Typical magnification of a light microscope, assuming visible range light, is up to 1500× with a theoretical resolution limit of around 0.2 μm or 200 nm. Electron microscopes were developed due to the limitations of light microscopes which are limited by the physics of light to 500× or 1000× magnification and a resolution of 0.2 micrometers. In the early 1930s, this theoretical limit had been reached, and there was a scientific desire to see the fine details of the interior structures of organic cells. This required 10,000× plus magnification which was just not possible using light microscopes.

11.2 Morphological and Anatomical Examination of Crude Drugs

Botanical identity of crude drugs can be achieved by macro- and microscopic examinations using hand lens, simple or compound microscope. Voucher specimens are reliable reference sources. Outbreaks of diseases among plants may result in changes to the physical appearance of the plant and lead to incorrect identification. At times, an incorrect botanical quality with respect to the labeling can be a problem. For example, in the 1990s, a South American product labeled as 'Paraguay Tea' was associated with an outbreak of anticholinergic poisoning in New York. Subsequent chemical analysis revealed the presence of a class of constituents that was different from the metabolites normally found in the plant from which Paraguay tea is made.

Morphological features or macroscopic characteristics of various plant organs like leaves, flowers, seeds, fruits, barks, root, rhizome, tubers, etc., are considered in the identification of crude drugs. These are organized drugs (with cellular structure), and there are unorganized (with acellular structures). Morphological characteristics of a drug may be divided into four headings viz. (i) shape and size, (ii) color and external markings, (iii) fracture and internal color, and (iv) odor and taste. Morphological features for the identification of leaves include their size, shape, type (simple, compound), sessile or petiolate, glabrous or hairy, if hairy, types of hairs (trichomes) present, type of venation, margin, apex, and base. Flowers can be identified partly by the nature of the inflorescence, partly by the nature of the various floral parts (calyx, corolla, filament, anther, stigma), their external features, and the structure of the perianth (sympetalous, actinomorphic, zygomorphic), and partly by the carpels (monocarpous, apocarpous, syncarpous). Seeds are usually identified by their size, shape, and external color, as well as by the form, arrangement, relative development of the embryo and its parts, and various markings (wrinkles, hilum, and raphe) and outgrowths (hairs, warts) on the surface. Features of fruits for their identification include type (simple, compound, aggregate, capsule, legume, berry), condition (dry, fresh, succulent, ripe, green), shape, size, and external markings (scars, rough, wrinkled). Barks are identified by their form (flat, curved, quailed), size (small pieces, big pieces), external markings (fissures, furrows, wrinkles, corrugations, lenticels), and presence or absence of cork, epiphytes (lichens, moss, etc.). Common features considered in the identification of roots, rhizomes, and tubers include shape (cylindrical, conical, fusiform, napiform), size (length and diameter), presence or absence of aerial parts, condition (woody, fleshy, succulent), and external markings.

In entire form, the drug is kept without any spectacular change in the natural gross morphology. This form is common in cases of seeds, flowers, fruits, leaves, and some roots and rhizomes; or they may be cut, broken, or sliced, as in woods, barks, many roots, and a few rhizomes. They may be more or less matted together, as in Chondrus and in baled leaves; they may be pressed together by hydraulic pressure giving the so-called pressed drugs, or they may be powdered and then

molded into forms, as rhubarb fingers. Drugs derived from underground parts of the plant, such as rhizomes, roots, bulbs, corms, and tubers, may be either (i) entire, (ii) in longitudinal slices, (iii) in oblique or transverse slices, (iv) cut in small cubical pieces, or (v) broken into pieces. Sometimes the periderm is removed, as in roots (Russian Licorice), rhizomes (Ginger), and barks (Sassafras). Mexican Sarsaparilla may come to the market in neat cylindrical rolls in which a mass of the bundled roots is tightly wrapped by many coils of long roots, or the roots may be in tightly packed bales, or it may be cut into short pieces, or be coarsely ground or finely powdered: Each of these forms presents a very different appearance, yet all are the same drug.

Barks are tissues in a woody stem outside the inner fascicular cambium, e.g., Cinnamon, Cinchona, Quillaia, Ashoka, and Kurchi. Underground drugs are often swollen due to storage of carbohydrates and other chemicals, e.g., roots (Podophyllum, Liquorice, Jatamansi, Rauwolfia), rhizomes, and stolons have buds, scale leaves, and scars (Ginger, Turmeric, Dioscorea). Leaves arise from a node on a stem and leafy drugs like Senna, Tulsi, Vasaka, Digitalis, etc., and leaves can be easily identified on the basis of their shape, margin, base, apex, and venation. Flowers possess different shapes, size, and color, e.g., Saffron, Banafsha, Pyrethrum. Fruits arise from the ovary and contain seeds, e.g., Cardamom, Colocynth, Almond, Vidang, Bahera, Amla, and Bael. Seeds are developed from the ovules in carpels of the flowers and characterized by the hilum, micropyle, and sometimes raphe. The seed drugs are Ispaghula, Linseed, Nux-vomica, Psoralia. Herbs are the whole aerial part, and it is sometimes used as a drug, e.g., Brahmi (*Bacopa monnieri*), Chirata (*Swertia chirata*), Kalmegh (*Andrographis paniculata*), Pudina (*Mentha arvensis*), Shankhpushpi (*Convolvulus pluricaulis*). The shape of a drug may be cylindrical (Sarsaparilla), subcylindrical (Podophyllum), conical (Aconite); fusiform, ovoid or pyriform (Jalap), and terete (tapering gradually) or disk-shaped (Nux-vomica). The drug may be simple, branched, curved, or twisted. The length, breadth, and diameter are measured in millimeters or centimeters. In case of conical drugs, the size of both parts is mentioned.

The parts may be simple or branched and are frequently curved and twisted. In the case of rhizomes, the direction of growth is often considered. This is usually horizontal but may be oblique and in a few cases is vertical. The direction may be roughly determined by the attachment of the roots and stem bases. Sizes are given as to length and diameter and in the most convenient terms, either millimeters (mm) or centimeters (cm). In cases where the shape is conical, the diameter of both wide and narrow parts may be of importance. External markings are classified as furrows, alternating ridges and valleys formed due to shrinkage of internal parts after drying; wrinkles, delicate furrows; annulations, transverse ring-like markings; fissures, splits extending into tissues; nodules, rounded outgrowth on the surface; projections of root, stem bases and buds; scars of leaf, stem-base, root, bud, bud-scale, etc. The fractures may be complete, incomplete, short, fibrous, splintery (breaking irregularly), brittle (easily broken), tough, and weak.

Anatomical or microscopic examination is an important technique, and all modern optical microscopes are designed for viewing samples by transmitted light

and magnify smaller objects and thus help to study their details—structure, constitution, and inclusions of plant parts and animal tissues. Microscopic evaluation is indispensable in the initial identification of herbs, as well as in identifying small fragments of crude or powdered herbs, and detection of foreign matter and adulterants. A primary visual evaluation, which seldom needs more than a simple magnifying lens, can be used to ensure that the plant is of the required species and that the right part of the plant is being used. At other times, microscopic analysis is needed to determine the correct species and/or that the correct part of the species is present. For instance, pollen morphology may be used in the case of flowers to identify the species, and the presence of certain microscopic structures such as leaf stomata can be used to identify the plant part used. Although this may seem obvious, it is of prime importance, especially when different parts of the same plant are to be used for different treatments. Stinging nettle (*Urtica urens*) is a classic example where the aerial parts are used to treat rheumatism, while the roots are applied for benign prostate hyperplasia.

A number of criteria need to be met for the development of microscopic characterizations relevant to botanical identification such as (i) the samples used for the characterizations must be accurately identified by a botanist; (ii) a variety of samples must be used and compared to ensure that the characterization encompasses the natural intraspecies variations that can occur, and (iii) the samples must be representative of the commercial material available in trade. The development of 'Botanical Microscopic Atlas' is to be based on the characteristics of multiple samples that are botanically authenticated, compared against botanical samples in professional herbaria, and cross-checked against other microscopic characterizations for consistency and completeness.

Each microscopic characterization is to be listed primarily according to the Latin botanical binomial nomenclature, including the botanical authority. The botanical nomenclature is then followed by the common name according to Herbs of Commerce (McGuffin et al. 2000), the corresponding pharmaceutical name, and the plant family, which in some cases is diagnostically valuable.

In addition to nomenclature, each microscopic characterization includes four parts: (i) a brief introductory paragraph on the primary medicinal use of the botanical with specific information on potential adulterants of which the microscopist should be aware; (ii) a detailed text description of the microscopic characterization of the plant part in its relatively whole form, along with a listing of the primary tissues found in the same material when it is powdered; (iii) illustrations of the primary tissues that are most prominent and diagnostically relevant to the microscopist; and (iv) photographic images of the primary structures and tissues. The illustrations allow key elements to be highlighted, and the images provide a view of what is actually seen by the microscopist.

11.3 Physical Constants: Techniques and Microscopic Measurement

The characteristic microscopic features include trichomes, palisade and spongy parenchyma, collenchyma, stomatal frequency, their index, shape and size, as well as vascular bundles, xylem and phloem cells, inclusions, etc., and their physical constants for leafy drugs while cork cambium, primary cortex, phloem fibers, medullary rays, endodermis, pericycle, vascular bundles, etc., in the transverse and longitudinal sections, and their physical constants stand as characteristic microscopic features of drugs from root, stem, etc. In powder materials, presence of cortex cells, sieve tubes, calcium oxalate crystals, lignified fibers, etc., are considered characteristic microscopic features. They are considered for both qualitative (study of thin sections or powder of leaf, stem or root, etc.) and quantitative (determination of stomatal number, stomatal index, vein-islet, vein termination number, palisade ratio, etc.) microscopy.

Microscopic examination of section and powder drugs aided by stains helps in distinguishing anatomy of adulterants. Microscopic examination of epidermal trichomes and calcium oxalate crystals is valuable in powdered drugs. In the powdered drugs, the cells are mostly broken, except lignified cells, and the cell contents like starch, calcium oxalate crystals, aleurone, etc., are scattered in the powder. Some fragments are specific for each powder which may consist of parts of cells or groups of cells. Plant parts are made up of specific arranged tissues, spores (Lycopodium), or hairs (Lupulin).

Histological characters are studied from very thin transverse or longitudinal sections properly mounted in suitable stains, reagents, or mounting media. The size, shape, and relative positions of the different cells and tissues, chemical nature of the cell walls and of the cell contents are determined. The basic arrangement of tissues in each drug is fairly constant. Fibers, sclereids, tracheids, vessels, and cork are least affected by drying. Starch, calcium oxalate, epidermal trichomes, and lignin are examined carefully.

Microscope is also used for a quantitative evaluation of drugs and adulterated powders. This is done by counting a specific histological feature such as stomatal index, vein-islets, and vein termination numbers, palisade ratio, etc. These features are compared with the standard samples. Palisade ratio: The average number of palisade cells beneath each epidermal cell is called as palisade ratio. It is determined from powdered drugs with the help of camera lucida.

Importance of the microscope as a tool for the study and analysis of crude drugs became obvious when Jacob Schleiden successfully utilized microscope in 1857 to distinguish various types of Sarsaparilla (*Smilax officinalis* and six other species of *Smilax* of Smilacaceae, native to South America, Jamaica, the Caribbean, Mexico, Honduras, and the West Indies) roots by means of their endodermal cells. Schacht also showed its value in 1953 in the examination of textile fibers. At present, it is one of the most commonly used optical instruments in the study of crude plant drugs.

The microscopic evaluation of drugs is done with the aid of microscopes and utilizes various microscopic characters of the drugs such as trichomes, calcium oxalate crystals, starch grains, pollen grains, etc., and their histological features such as types and arrangements of various cells and tissues. This method of evaluation is indispensable in the evaluation of powdered drugs, as they possess very few macroscopic characters other than color, odor, and taste. Microscope is also essential for determining some important physical constants like stomatal number, stomatal index, palisade ratio, vein-islet number, vein termination number, etc., of leaf drugs. This type of microscopic determinations is otherwise known as quantitative microscopy.

Microscope is useful in both the qualitative and quantitative study and analysis of crude drugs. For qualitative microscopy, transverse sections of leaf and transverse and longitudinal sections of stem and root including their barks are studied under photomicrograph. Leaf microscopy involves the study of external and internal structure and characteristics of lamina (isobilateral or dorsiventral). Color and presence of oil glands in the lamina are also taken into consideration for study. For internal structure, leaf color and pigments are removed by using suitable reagents (e.g., chloral hydrate solution), freehand thin sections are taken by inserting a suitable leaf segments in a potato cube, then mounted on a glass slide in glycerin without or with stains (e.g., methyl orange and phloroglucinol-HCl) as per standard procedures (Wallis 1985; Kokate 2005; Ali 2008; Pandya et al. 2010). Different identifying characters of epidermis, epidermal outgrowth (trichome) and modification (stoma), mesophyll tissue, palisade and spongy parenchyma ratio, vascular bundle (xylem, phloem, cambium and bundle sheath), etc., are then studied for quantification under microscope fitted to camera lucida. For the internal structure of bark, it is softened by boiling in water for few minutes in a test tube containing sufficient water and was boiled for few minutes, and then the softened bark is sliced into fine sections transversally and longitudinally. The stained and unstained sections may be observed under microscope for the identifying characters (Khandelwal 2007; Gupta et al. 2008).

For powder microscopy, a little quantity of the dried powdered material is to be taken onto a microscopic slide, stained by using a little quantity (1–2 drops) of different staining reagents (such as iodine for detection of starch grains, calcium oxalate crystal, and phloroglucinol-HCl solution for detection of lignified components), covered with a cover slip and then studied under microscope the characteristic structures after mounting the preparation in glycerol. The presence of starch grain and calcium oxalate crystal was detected by the formation of blue color on addition of 2–3 drops of 0.01 M iodine solution (Thitikornpong et al. 2011)

Minute morphological structures (trichomes, glands, stomata, calcium oxalate crystals, etc.) of plant organs and their dimensions are very conveniently studied and measured under the microscope. These structures and their sizes are often very useful in the identification of crude plant drugs. Histological structures, which are most frequently used to identify most natural crude drugs and to detect adulterants in them, can only be studied under the microscope in thin sections and in powders. The microscope is indispensable in the identification of powdered drugs and

detection of adulterants in them as they possess very few macroscopic characters other than color, odor, and taste.

Qualitative characters like types of stomata found in different leafy drugs would be the diagnostic characters of different drugs, e.g., (i) paracytic or rubiaceous or parallel-celled stomata in leaf of coca, senna; (ii) diacytic or caryophyllaceous or cross-celled stomata in peppermint, vasaka; (iii) anisocytic or cruciferous or unequal-celled stomata in Belladonna, Datura; and (iv) anomocytic or ranunculaceous or irregular-celled stomata in Digitalis, Lobelia.

Trichome is an elongated tubular outgrowth of an epidermal cell and its function may be protective and also it secretes essential oil and absorbs water. Different types of trichomes are associated with different crude drugs, e.g., (a) covering or non-glandular trichomes [(i) lignified trichomes, (ii) short, sharp pointed, curved, (iii) large, conical, strongly shrunken, (iv) short, conical, warty] in Nux-vomica, Strophanthus, Cannabis, Lobelia, Senna; (b) covering trichomes (multicellular T-shaped trichomes) in Artemisia, Pyrethrum; (c) covering unbranched trichomes [(i) bi-cellular, conical, (ii) three-celled long, (iii) four- to five-celled long)] in Datura, Stramonium, Belladonna; (d) glandular trichomes [(i) unicellular, (ii) multicellular)] in Vasaka, *Digitalis pupurea*, *D. thapsi*, *Cannabis sativa*.

Types or shapes of cell inclusions or ergastic substances like calcium oxalate crystals as seen under the light microscope may often be the distinguishing feature of many crude drugs, e.g., (i) microphenoidal in Belladonna, (ii) prism in Hyoscymus and senna, (iii) raphides in Squill, Rauwolfia, and Cinnamon, and (iv) rosetts in senna, Rhubarb, and acicular crystals in Squill, Ipecacauanha.

Physical constants (leaf constants) like (i) **Palisade ratio**: average number of palisade cell beneath each epidermal cell, it can be determined with powdered drugs; (ii) **vein-islet number**: number of vein-islets per sq. mm of the leaf surface midway between midrib and margin; (iii) **vein termination number**: number of vein-islets termination per sq. mm of the leaf surface midway between midrib and margin; (iv) **stomatal number**: average number of stomata per sq. mm of epidermis of the leaf; and (v) **stomatal index**: percentage which the number of stomata forms to the total number of epidermal cells each stoma being counted as one cell. These are conveniently determined by quantitative microscopy only. These are valuable parameters in the identification and purity determination of crude plant drugs, particularly leaf drugs. Drawing of internal structures of plant and animal organs and various other minute structures to scale and in their exact natural shape and arrangement is done under the microscope. It is also used for quantitative microanalysis of admixed or adulterated powdered drugs.

Palisade ratio represents the average number of palisade cells beneath one epidermal cell, using four continuous epidermal cells for the count. It is determined from powdered drugs with the help of camera lucida. Plisade ratio of *Atropa belladonna*—05–07; *Adhatoda zeylanica*—5.5–6.5; *Cassia angustifolia*—5.5–10 upper, 4.0–7.4 lower (senna); *Digitalis lanata*—2.5–6.5, etc.

For the determination of palisade ratio, a piece of the leaf boiled in chloral hydrate is placed on a slide under microscope. Camera lucida and drawing board are arranged and the outline of four cells of the epidermis is to be traced using 4 mm

objective. Then, palisade layer is focused down, and sufficient cells for covering the tracing of the epidermal cells are traced off. The outline of those palisade cells which are intersected by the epidermal walls is completed. The palisade cells under the four epidermal cells (including cells which are more than half and excluding cells which are less than half within the area of epidermal cells) are counted. The determination for five groups of four epidermal cells from different part of the leaf is to be repeated. The average number of cells beneath epidermal cells calculated is known as palisade ratio.

Stomatal number is calculated as the average number of stomata per square mm of the epidermis. Stomatal number of *Atropa belladonna* were: 07–10 (upper epidermis), 77–115 (lower epidermis); *Datura metel* were: 147–160 (upper epidermis), 200–209 (lower epidermis); and *Ocimum sanctum* were: 64–72 (upper-dermis), 175–250 (lower epidermis).

Stomatal index (SI) is the percentage proportion of the number of stomata to the number of total epidermal cells. For determination of stomatal index (S.I.), a piece of leaf is to be cleaned, and the upper and lower epidermis is to be peeled out separately by means of forceps, put on slide and mounted in glycerin (10%) and studied under microscope. Camera lucida is attached, and drawing board is placed for drawing the cells. A square of 1 mm by means of stage micrometer may be drawn on it. The number of stomata and the number of epidermal cells in each field or focus may be counted and averaged, and the stomatal index may be calculated by using the appropriate formula separately for upper and lower surface.

Stomatal index (S.I.) can be calculated by using the following formula:

$$\text{S.I.} = S/S + E \times 100$$

where S = number of stomata per unit area and E = number of epidermal cells in the same unit area.

S.I. of *Atropa belladonna* is 20.2–23.0. Stomatal number varies with the age of a plant but the S.I. for a given plant species generally remains constant throughout the age.

Vein-islet number is the number of vein-islets per sq. mm of leaf surface (photosynthetic tissue) encircled by the ultimate divisions of the conducting strands. Vein-islet number is calculated from four contiguous sq. mm in the central part of the lamina, midway between the midrib and the margin. The ranges of vein-islet in different drug plants vary considerably, e.g., *Andrographis paniculata*—9–12; *Bacopa monniera*—6–13; *Cannabis sativa*—18.24; *Digitalis purpurea*—2.5–3.0; *Eucalyptus globules*—8–13.5; *Cassia senna*—26; *C. angustifolia*—21; *Erythroxylum coca*—11, *E. iruxiuense*—20. Vein termination number is the number of veinlet termination per sq. mm of the leaf surface between midrib and margin. A vein termination is the ultimate free termination of a veinlet or branch of a veinlet. By this character, different coca leaves and senna leaflets are differentiated.

Determination of vein-islet and vein termination number is also considered in quantitative microscopy for herbal drug authentication. Vein-islet is the minute area

of photosynthetic tissue encircled by the ultimate division of the conducting strands. Vein termination number is the number of veinlet terminations per mm of leaf surface. For determination, a piece of the leaf is cleared by boiling in chloral hydrate solution, and camera lucida and drawing board are arranged, and 1 mm line is drawn with help of stage micrometer. A square is to be constructed on this line in the center of the field. The slide is to be placed on the stage. The veins included within the square are to be traced off, completing the outline of those islets which overlap two adjustment sides of the square. The average number of vein-islet from the four adjoining square, to get the value for one square mm, is calculated (Srinivasa et al. 2008). The number of veinlet termination present within the square is counted, and the average number of veinlet termination number from the four adjoining square to get the value for 1 square mm is found known as vein termination number.

Lycopodium Spore Method

Lycopodium is a Pteridophyte plant that has small spore-carrying cones. The number of spores per mg of Lycopodium powder was determined by (a) direct counting and (b) calculation based on specific gravity and dimensions of the spores which gave values in good agreement. As a quantitative microscopic method, Lycopodium spore method is considered for the study of powdered drugs having well-defined particles like pollens, starch grains, single-layered tissues, or some other types of uniformly thick particles. This is an important method employed, especially in identification of *Caryophyllus aromaticus* when chemical and physical methods are inapplicable as accurate measures of quality. On average, uniform size ($\sim$ 25 um) 94,000 spores per mg of powdered Lycopodium are present. By using Lycopodium spore method, the percentage purity of authentic powdered drugs such as ginger (*Zingiber officinale*) can be calculated by using the following equation as:

$$\text{Percentage purity of drug} = (N \times W \times 94{,}000/S \times M \times P) \times 100;$$

where

N number of characteristic structures (e.g., starch grains),
W weight in mg of Lycopodium taken,
S number of Lycopodium spores in the same 25 fields,
M weight in mg of sample calculated on the basis of dried sample at 105 °C, and
P 2,86,000 in case of ginger starch grain powder.

By employing Lycopodium spore method, the number of pollen grains in Pyrethrum powder (1000–2000/mg) and starch granules in wheat powder (400 granules/mg) has been determined. Lycopodium spore method is also useful for the determination of size of a particular type of particle in powders such as epidermal fragments of leaves, single layer of sclerenchyma, or isolated fibers (e.g., epidermal area of Indian senna stalk, sclerenchyma layer in linseed, fibers in the Cinnamon bark) can be measured. The procedure is almost the same as used for counting of particles. The particle size is traced with the help of camera lucida, and the spores

are counted. The tracings are cut out and weighed and their area calculated by weighing a sheet of known area of the paper used. This area divided by the magnification used gives the actual area of the particles in a certain weight of the powdered drug, which is calculated from the number of spores counted and the weight of spores and powder in the suspension. Drawing of internal structures of plant and animal organs and various other minute structures to scale and in their exact natural shape and arrangement is done under the microscope. It is also used for quantitative microanalysis of admixed or adulterated powdered drugs.

11.4 Microscopic Authentication and Quality Assessment of Herbal Drugs

Macroscopic examination can easily be employed to determine the presence of foreign matter, although microscopy is indispensable in certain special cases (e.g., starch deliberately added to dilute the plant material). Determination of foreign matter ensures that the stated herbal drugs are made from the specific part of the plant and are devoid of other parts of the same plant or other plants. They should be entirely free from molds or insects, including excreta and visible contaminant such as sand and stones, poisonous and harmful foreign matter and chemical residues. Animal matters such as insects and invisible microbial contaminants, which can produce toxins, are also among the potential contaminants of herbal medicines. Furthermore, when foreign matter consists, for example, of a chemical residue, TLC is often needed to detect the contaminants.

Standardization of herbal drugs is necessary for the establishment of their identity, purity, safety, and quality. Microscopic method of standardization is one of the cheapest and simplest methods to start with establishing the correct identification of the source material (Singh et al. 2010) and evaluation of purity of drugs (Kumar et al. 2011a, b). Microscopic parameters are distinctive enough to identify and determine the authenticity of herbal drugs and may be included as microscopic standards in the text of Herbal Pharmacopeia. Upton et al. (2011) by putting emphasis on the importance of authoritative microscopic descriptions of the commercially used medicinal plant species for correct identification, provided an atlas containing detailed text and graphic descriptions of more than 140 medicinal plant species and their adulterants. All these may definitely fulfill the needs of the herbal products industry, regulatory agencies, and academic researchers.

Internal structures or histological or anatomical characters (e.g., microscopic structures and measurements) of crude drugs are very valuable in the confirmation of their identities. Drugs which look very similar in their gross morphology differ sufficiently in their histology—thus making it possible to differentiate between them and to identify them correctly. Microscopic structures are most valuable, especially in the identification of powdered drugs as their identification is largely based on the form, the presence, or absence of certain cell type and cell inclusions. The structures

of histological elements as well as the size of individual elements vary in different plants. Measurements of these elements or structures (fibers, stone cell, vessels, trichomes, starch grains, oxalate crystals, etc.) are often of considerable importance in the identification of the source of the drugs.

Microscopical studies involving the quantitative determination of stomatal number, stomatal index value and palisade ratio, vein-islet and vein termination value determination are important in the evaluation of crude drugs. The information obtained from preliminary phytochemical screening will be useful in finding out the quality of the drug and, in addition to that, microscopic as well as morphological studies will provide reliable information for detecting adulteration. To ensure identification of the crude drugs, microscopic analysis should be supplemented with physicochemical analysis of the plant material.

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Chapter 12
Intellectual Property (IP) and Intellectual Property Right (IPR), Traditional Knowledge (TK) and Protection of Traditional Medical Knowledge (TMK)

Abstract Intellectual property (IP), creations of the mind, has both a moral and a commercial value. Traditional medical knowledge, such as the medicinal use of herbs, is often associated with genetic resources. Herbal genetic resources exist in nature and are not creations of the human mind; therefore, they cannot be directly protected as intellectual property (IP). They are subject to access and benefit-sharing regulations under international agreements. Patents based on traditional Indian medicine have included the use of turmeric for healing wounds; the antifungal properties of neem and a diabetes medicine made from extract of black plum (*Syzygium cumini*) were subsequently revoked. IP includes inventions, literary and artistic works, designs and symbols, names and images used in commerce. IP is protected by patents, copyright, trademarks, trade secret, geographical indication, etc. IP law grants the author of an intellectual creation exclusive right for exploiting and benefiting from their creation. Intellectual property right (IPR) is a right of a person or a company to have exclusive authority over the use of its own plans, ideas, or other intangible assets without the worry of competition. This right safeguards creators and other producers and may be enforced by a court via a lawsuit. The plant variety protection and farmers rights act enacted in many countries of the world was designed to protect the new plant and crop variety. On April 26 every year, we celebrate World Intellectual Property Day to promote discussion of the role of IP in encouraging innovation and creativity. According to Article 27 of the Universal Declaration of Human Rights, "everyone has the right to the protection of the moral and material interests resulting from any scientific, literary, or artistic production of which he is the author". The ethical problems brought up by intellectual property rights are most pertinent when it is socially valuable goods like life-saving medicines and genetically modified seeds that are given intellectual property protection. Traditional knowledge (TK) about the use of medicinal herbs of many nations is highly valuable. TK of various communities has even led to discovery and development of drugs like digitalis, morphine, colchicine, artemisinin, podophyllotoxin, salicin, etc., from various plant species. Biodiversity rich regions of various continents across the globe harbor flora of immense medicinal importance. The fastest growing international drug market for botanical medicines has seriously affected many species almost to the level of extinction because many of their ruthless

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exploitation in an unsystematic manner. The traditional knowledge is drawing global attention, popularity, and patronization due to awareness regarding the side effects of allopath but this has made the traditional knowledge system prone to 'biopiracy' and 'patenting' both within the country of origin as well as outside. The false claim on novelty and use of indigenous knowledge for commercial benefits needs to be checked. It is essential not only to preserve the traditional and indigenous knowledge but also to preserve the biodiversity of a locality and culture of the indigenous people from wrongful ownership. The major International Regulations effecting IPRs and traditional knowledge are Convention on Biological Diversity (CBD) and Trade-Related Intellectual Property Rights (TRIPs). The provisions of TRIPs and CBD have tried to develop a system of protection of traditional knowledge globally, which needs to be further strengthened in terms of providing incentives for disclosure and dissemination of valuable traditional knowledge. The disclosure and dissemination of traditional knowledge is to be achieved by linking the grassroots knowledge systems with the global opportunities for financing the commercial use of biological diversity. The developing countries have a rich abundance of indigenous and local knowledge systems, and documentation of this knowledge is of prime importance. This documentation in electronic format would serve as a databank for searching for information before grant of patent and would register the traditional use patterns.

Keywords Intellectual property (IP) · Intellectual property right (IPR) · Traditional knowledge (TK)

12.1 Intellectual Property (IP) and Intellectual Property Right (IPR)

12.1.1 Intellectual Property (IP)

Intellectual property (IP) refers to creations of the mind, which have both a moral and a commercial value. IP includes such events as inventions; literary and artistic works; designs; and symbols, names, and images used in commerce. IP is protected in law by, e.g., patents, copyright, and trademarks, which enable people to earn recognition or financial benefit from what they invent or create. By striking the right balance between the interests of innovators and the wider public interest, the IP system aims to foster an environment in which creativity and innovation can flourish. IP law typically grants the author of an intellectual creation exclusive right for exploiting and benefiting from their creation. However, IP rights (monopoly right of exploitation) are limited in scope, duration, and geographical extent.

IP protection is intended to stimulate the creativity of the human mind for the benefit of all by ensuring that the advantages derived from exploiting a creation benefit the creator. This will encourage creative activity and allow investors in research and development a fair return on their investment. IP confers on

individuals, enterprises, or other entities the right to exclude others from the use of their creations. Consequently, intellectual property rights (IPRs) may have a direct and substantial impact on industry and trade as the owner of an IPR may—through the enforcement of such a right—prevent the manufacture, use, or sale of a product which incorporates the IPR. For this reason, control over the intangible asset (IPR) connotes control of the product and markets. IP protection encourages the publication, distribution, and disclosure of the creation to the public, rather than keeping it secret while at the same time encouraging commercial enterprises to select creative works for exploitation.

12.1.2 Intellectual Property Right (IPR)

Intellectual property right (IPR) is of a right person or a company to have exclusive authority over the use of its own plans, ideas, or other intangible assets without the worry of competition, at least for a specific period of time. Intellectual Property Rights are legal rights, which result from intellectual activity in industrial, scientific, literary, and artistic fields. These rights safeguard creators and other producers of intellectual goods and services by granting them certain time-limited rights to control their use. These rights may be enforced by a court via a lawsuit. The reasoning for intellectual property is to encourage innovation without the fear that a competitor will steal the idea and/or take the credit for it. Protected IP rights like other property can be a matter of trade, which can be owned, sold, or bought. These are intangible and non-exhausted consumption.

12.2 Types of Intellectual Property Right (IPRs)

Intellectual Property laws include (a) Patents, (b) Trademarks, (c) Copyrights, (d) Geographical Indications, (e) Industrial Designs, (f) Trade Secrets, (g) Layout Design for Integrated Circuits, and (h) Protection of New Plant Variety.

12.2.1 Patent

A patent is an exclusive right granted for an invention, and it provides protection for the invention and right to the patent owner to decide how and when the invention can be used by others. Patent protection means that the invention cannot be commercially made, used, distributed, or sold without the patent owner's consent. The protection is granted for a limited period. Once a patent expires, the protection ends, and an invention enters the public domain and becomes available to commercial exploitation by others. All patent owners are obliged to publicly disclose

information on their invention in order to enrich the total body of technical knowledge in the world. Such an ever-increasing body of public knowledge promotes further creativity and innovation in others and thus valuable information and inspiration for future generations of researchers and inventors.

12.2.2 Trademarks

A trademark is a distinctive sign capable of distinguishing the goods or services of one enterprise from those of other enterprises. Trademarks date back to ancient times when craftsmen used to put their signature or 'mark' on their products. It may be one or a combination of words, letters, and numerals or drawings, symbols, three-dimensional signs (shape and packaging of goods), audible signs (music or vocal sounds), fragrances, or colors used as distinguishing features. It provides protection to the owner of the mark by ensuring the exclusive right to use it to identify goods or services, or to authorize another to use it in return for payment. It helps consumers identify and purchase a product or service because its nature and quality, indicated by its unique trademark, meets their needs. Trademark rights (require registration) may be held in perpetuity but the initial term of registration is for 10 years, and thereafter, it may be renewed from time to time.

12.2.3 Copyrights and Related Rights

Copyright is a legal term describing rights given to creators for their literary (e.g., books, novels, poems, plays, reference works, newspapers) and artistic (e.g., paintings, drawings, photographs, and sculpture) works; films, musical compositions, and choreography; architecture; and advertisements, maps, and technical drawings to computer programs and databases. Copyright registration is not mandatory, and often, it is sold in exchange of royalties with a time limit (life of author plus 60 years after creator's death).

12.2.4 Geographical Indications (GI)

GI and appellations of origin are signs used on goods that have a specific geographical origin and possess qualities, a reputation or characteristics that are essentially attributable to that place of origin (a village or town, a region or a country). A geographical indication includes the name of the place of origin of the goods, and since the qualities depend on the geographical place of production, there is a clear link between the product and its original place of production. Quality of agricultural product is derived from their place of production and influenced by

specific local environmental factors (climate and soil), human factors (manufacturing skills and traditions), etc. A geographical indication is an exclusive right given to a particular community; hence, the benefits of its registration are shared by the all members of the community. Geographical indications are typically used for agricultural products, foodstuffs, wine, and spirit drinks, handicrafts, and industrial products. Bordeaux (wine), Vodka (wine), Darjeeling (tea), Tuscany (olive oil), Muga Silk, etc., are some well-known examples of GIs. GIs of goods like Muslin, Tangail Sarees, Rajshahi Silk, Embroidered Quilt, Fazlee Aam (a high-quality mango of Rajshahi), Commilla Khoddor (handicraft), Bogra Dodhi (yogard), etc., of Bangladesh are mentionable. GIs are usually protected by sui GENERIS systems (i.e., special regimes of protection), using collective or certification marks, and focusing on business practices, including administrative product approval schemes.

12.2.5 Industrial Designs

An industrial design refers to creative activity and constitutes the ornamental or aesthetic aspect of an article. A design right refers to a novel or original design and may consist of three-dimensional features, such as the shape or surface of an article, or of two-dimensional features, such as patterns, lines, or color that is accorded to the proprietor of a validly registered design. Industrial designs are an element of intellectual property. The essential purpose of design law is to promote and protect the design element of industrial production. It is also intended to promote innovative activity in the field of industries.

12.2.6 Trade Secrets

It may be confidential business information (manufacturing or industrial secrets and commercial secrets) and include sales methods, distribution methods, consumer profiles, and advertising strategies, lists of suppliers and clients, and manufacturing processes. Contrary to patents, trade secrets are protected without registration. The trade secret and traditional knowledge are also interlinked/associated with the geographical indications.

12.2.7 Layout Design for Integrated Circuits

Semiconductor Integrated Circuit means a product having transistors and other circuitry elements (Chip Layout Designs), which are inseparably formed on a semiconductor material or an insulating material or inside the semiconductor

material and designed to perform an electronic circuitry function. The initial term of registration is for 10 years; thereafter, it may be renewed from time to time.

12.2.8 Protection of New Plant Variety

The objective of this act is to recognize the role of farmers as cultivators and conservers and the contribution of traditional, rural, and tribal communities to the country's agro-biodiversity by rewarding them for their contribution and to stimulate investment for R&D for the development of new plant varieties to facilitate the growth of the seed industry.

The Plant Variety Protection and Farmers Rights act 2001 that came into force on 30.10.2005 initially included 12 crop species (e.g., Rice, Wheat, Maize, Sorghum, Pearl millet, Chickpea, Green gram, Black gram, Lentil, Kidney bean, etc.), and India opted for sui-generic system instead of patents for protecting new plant variety.

Intellectual property rights connected with the use of traditional medicinal plants (bioresources) have been debated worldwide. However, the convention on Biological Diversity (CBD), signed in Rio in 1992, enforces protection of the rights of local people and local knowledge as well as conservation of the biological resources.

Ethics

The ethical problems or issues sorrounding intellectual property rights are most pertinent when it is socially valuable goods like life-saving medicines and genetically modified seeds are given intellectual property protection. For example, the application of intellectual property rights allows pharmaceutical companies to prevent other companies from manufacturing their product without the additional cost of research and development, and companies charge higher than the marginal cost of production in order to recoup the costs of research and development. An IPR-driven regime is therefore not a regime that is conductive to the investment of R&D of products that are socially valuable to predominately poor populations.

12.3 Traditional Knowledge (TK), Traditional Medical Knowledge (TMK), Genetic Resources, Traditional Knowledge Digital Library and Protection of Traditional Medical Knowledge

12.3.1 Traditional Knowledge (TK)

Traditional knowledge (TK) includes tradition-based literary, artistic and scientific works, performances, inventions, scientific discoveries, designs, marks, names and symbols, undisclosed information, and all other tradition-based innovations and

creations resulting from intellectual activity in the industrial, scientific, literary, or artistic field (WIPO 2001, 2002). TK is generally considered the collective heritage of a particular indigenous people or local community. While individuals, such as a *shaman* in Bolivia or a *sangoma* in South Africa, may themselves innovate, what makes their innovations traditional is that they are based on the community's collective heritage, and the innovations are regarded as community-held. Traditional knowledge is created in a manner that reflects community traditions; it is often intergenerational and created and held collectively. TK provides a pathway to social and economic development such as the Seri people of Mexico use the *Arte Seri* mark to distinguish their craftworks based on their TK and associated genetic resources, and to support a sustainable trade in these products. Traditional ecological knowledge held by aboriginal communities in Canada has proven to be valuable in environmental planning and resource management. Other examples of TK include: (i) Sustainable irrigation is maintained through traditional water systems such as the *aflaj* in Oman and Yemen, and the *qanat* in Iran, (ii) Cree and Inuit maintain unique bodies of knowledge of seasonal migration patterns of particular species in the Hudson Bay region, and (iii) *Oryza longistaminata* is a wild rice grows as weed in the marshes and river banks of Mali. The *Bela* community developed detailed knowledge of its agricultural value, recognized its stronger resistance to diseases (blight) than many other local rice. Guided by this TK, researchers subsequently isolated and cloned a gene named Xa21, which conferred this resistance in rice plants. TK holders stress that their TK should not be used by others inappropriately, without their consent and arrangements for fair sharing of the benefits and urge for greater respect and recognition for the values, contributions, and concerns of TK holders. The protection of TK is often closely linked to protection of biodiversity, in particular under the Convention on Biological Diversity (CBD).

Traditional does not necessarily mean old but it is related to the way in which the knowledge is created, preserved, and transmitted. It is evolving all the time, a process of periodic, even daily creation as individuals and communities take up the challenges presented by their social and physical environment. In many ways, traditional knowledge is actually contemporary knowledge but embedded in traditional knowledge systems, which each community has developed and maintained in its local context. TK is a living body of knowledge that is developed, sustained, and passed on from generation to generation within a community, often forming part of its cultural or spiritual identity. Figure 12.1 represents the relationship between the concepts of heritage, TK and associated characters and their relative conceptual boundaries (WIPO 2001).

TK has wider significance and invites international discussions on different issues such as food and agriculture, biological diversity, desertification and the environment, human rights including the rights of indigenous peoples, cultural diversity and trade, and economic development. The WIPO Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore (IGC), as an international policy forum, works with other international agencies against misuse or misappropriation of TK (WIPO 2001).

Fig. 12.1 Relationship between the concepts of heritage, TK, etc., and their relative conceptual boundaries (from WIPO 2001)

12.3.2 Traditional Medical Knowledge (TMK)

Traditional medical knowledge (TMK) is the knowledge of the therapeutic use of herbs and other natural resources as well as some procedures that were developed by tradition from prehistoric times. Traditional medicine (medicaments from natural sources used traditionally) is used worldwide, e.g., ~80% of the population many developing countries of Asia and Africa depend on traditional medicine for primary health care, and ~70 to 80% of the population use traditional medicine in some forms of alternative or complementary medicine. Many modern drugs and vaccines are based on natural resources and associated traditional knowledge. It has social, cultural, and scientific value and is important for many indigenous peoples and local communities. Growing commercial and scientific interest in traditional medicine systems has led to calls for traditional medical knowledge to be better recognized, respected, preserved, and protected. Some examples of TMK are: (i) Thai traditional healers use *plao-noi* to treat ulcers, (ii) indigenous healers in the western Amazon use the *Ayahuasca* vine to prepare various medicines, imbued with sacred properties. Traditional medical knowledge (medicinal use of herbs) is often associated with genetic resources. For instance, calanolides, compounds derived from the latex of Calophyllum trees found in the Malaysian rainforest, are a potential treatment for HIV and certain types of cancer. Because genetic resources exist in nature and are not creations of the human mind, they cannot be directly protected as intellectual property (IP).

12.3.3 Genetic Resources (GRs)

Genetic resources (GRs) refer to genetic material of actual or potential value. Genetic material is any material of plant, animal, microbial, or other origin containing functional units of heredity. Examples include material of plant, animal, or microbial origin, such as medicinal plants, agricultural crops, and animal breeds.

GRs as found in nature are not creations of the human mind, and thus, they cannot be directly protected as intellectual property (IP). However, there are IP issues associated with GRs. Inventions or plant varieties based on or developed using GRs (associated with traditional knowledge or not) may be patentable or protected by plant breeders' rights. In considering IP issues associated with GRs, WIPO's work complements the frameworks for access and benefit-sharing provided by the Convention on Biological Diversity (CBD) and its Nagoya Protocol, and the International Treaty on Plant Genetic Resources for Food and Agriculture of the United Nations Food and Agriculture Organization (FAO).

Negotiations on an international legal instrument on IP issues related to GRs are taking place in the WIPO Intergovernmental Committee on Intellectual Property and Genetic Resources, Traditional Knowledge and Folklore. Issues under discussion include:

(i) **Prevention of erroneously granted patents**: It is generally considered that the granting of patents over inventions based on or developed using GRs (and associated traditional knowledge) which do not fulfill the existing requirements of novelty and inventiveness should be prevented. To help patent examiners find relevant "prior art" and avoid the granting of erroneous patents, WIPO has improved its own search tools and patent classification systems, and it is proposed by some that databases and information systems related to GRs be created to address this issue. A disclosure requirement may also address this issue (see disclosure requirements table).

(ii) **Ensuring and tracking compliance with access and benefit-sharing frameworks**: Disclosure requirements are one of the proposals to address this issue. Disclosure requirements mean patent (and perhaps also other forms of IP applicants should disclose several categories of information concerning GRs, such as the source or origin of GRs and evidence of prior informed consent and benefit-sharing, when these GRs are used in developing the innovation claimed in a patent application.

12.3.4 Traditional Knowledge Digital Library (TKDL)

The grant of wrong patents linked to traditional medicines (based on traditional medical knowledge or a minor variation) has been causing a great concern to the developing world. India is pioneer in this field of development Traditional Knowledge Digital Library (TKDL). The Council of Scientific and Industrial Research (CSIR) of India when claimed for re-examination of patent No. US 5,401,504 granted to two US Indians related to wound-healing properties of turmeric, the US Patent and Trademark Office (US PTO) revoked this patent after ascertaining that there was no novelty, but based on the century old TMK of India. Similarly, the case of the revocation of the patent granted to W.R. Grace Company

and US Department of Agriculture on Neem (EPO patent No. 436,257) by European Patent Office.

Traditional Knowledge Digital Library (TKDL) is a pioneer initiative of India to prevent misappropriation of traditional medicinal knowledge (TMK) at International Patent Offices. Its genesis dates back to the Indian effort on revocation of patent on wound-healing properties of turmeric at the USPTO. TKDL has overcome the language and format barrier by scientifically converting and structuring the available contents of the ancient texts on Indian Systems of Medicines, i.e., Ayurveda, Siddha, Unani, and Yoga, into five international languages, namely English, Japanese, French, German, and Spanish, with the help of information technology tools and an innovative classification system—Traditional Knowledge Resource Classification (TKRC). TKDL has also been able to set international specifications and standards for setting up of TK databases based on TKDL specifications. This was adopted in 2003 by the Committee in fifth session of the Intergovernmental Committee (IGC) of WIPO on Intellectual Property and Genetic Resources, Traditional Knowledge and Expression of folklore.

12.3.5 Protection of Traditional Medical Knowledge

The World Intellectual Property Organization (WIPO) is primarily concerned with protection of TMK like IP against unauthorized use by third parties. The Intergovernmental Committee of WIPO on Intellectual Property, Genetic Resources, Traditional Knowledge, and Folklore (IGC) intend to develop an international legal instrument that would provide effective protection of traditional cultural expressions/folklore and traditional knowledge (including traditional medical knowledge). Protection of TMK against unauthorized use and misappropriation by third parties who have patented compounds derived from traditional medicines without the prior consent of traditional medical knowledge holders and without fair compensation is necessary.

Patents based on traditional Indian medicine (use of turmeric for healing wounds, the antifungal properties of *neem*, diabetes medicine made from extract of *jamun*, etc.) on the ground of unauthorized use of TMK have been revoked or invalidated. But for captopril (a drug used to treat hypertension and heart failure) no benefits have been allotted to the indigenous Brazilian tribe who first used pit viper venom as an arrowhead poison. The San people of the Kalahari Desert, on the other hand, have a benefit-sharing agreement on *hoodia* (an appetite-suppressant succulent plant) with South Africa's Council for Scientific and Industrial Research. Similarly, the Kani tribe of South India share in the benefits from a new sports drug named Jeevani (an antistress and antifatigue agent) based on their TMK from the herbal medicinal plant *arogyapaacha*. Indian scientists at the Tropical Botanic Garden and Research Institute (TBGRI) used the tribal know-how to develop the drug. The scientists isolated 12 active compounds from *arogyapaacha* and filed two patent applications on the drug, and the technology was then licensed to an Indian

pharmaceutical manufacturer pursuing the commercialization of Ayurvedic herbal formulations. A trust fund was established to share the benefits arising from the commercialization of the TK-based drug.

IP protection of TMK may be positive and defensive:

(i) Positive protection (recognition of IP rights in TK) grants IP rights over the subject matter of traditional medical knowledge. This may help communities to prevent others from gaining illegitimate access to traditional medical knowledge or using it for commercial gain without equitably sharing the benefits.
(ii) Defensive protection (safeguarding against illegitimate IP right over TK) does not grant IP rights over traditional medical knowledge but aims to stop such rights from being acquired by third parties. Defensive strategies include the use of documented TMK to preclude, oppose, or invalidate patents on claimed inventions. Defensive protection of TK has two aspects such as a legal aspect and a practical aspect.

12.4 Traditional Medicine, Herbal Products and IPRs

Traditional medicine is the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures used in the maintenance of health, as well as to prevent, diagnose, improve, or treat physical and mental illnesses. It is a comprehensive term and includes Traditional Chinese Medicine (TCM), Ayurvedic medicine, and Unani medicine, and other forms of indigenous medicine practiced traditionally. It is an elaborate set of indigenous knowledge that includes different therapeutic ideas, belief, products, and practices. Traditional medicine adopted by other people outside the indigenous culture is called complementary and alternative medicine (CAM) (WHO 2008).

Traditional medicines are consisted of herbs, herbal materials and preparations, and finished herbal products as well as animal and mineral products. Traditional medicines are used widely throughout the world, especially in developing countries for primary health care and in many developed countries in some form of CAM, such as acupuncture (WHO 2008).

Herbal treatments (treatment based on herbs and herbal products) is a most popular form of traditional medicine. International trade in traditional medicines is growing, and China alone exported herbal products of about US$1.8 billion in 2010 (Anonymous 2012). The use of traditional medicines is increasing gradually almost worldwide outside the confines of traditional cultures and areas. The WHO, in cooperation with its member states, promotes the rational use of traditional medicine for health care, monitors the status of traditional medicine around the world, and has published a worldwide review to facilitate the development of legal frameworks and the sharing of experiences between countries.

12.4.1 Traditional Medical Knowledge in International Health and IP Policy

TK in a broad sense include many contexts, e.g., environment and biodiversity, health, human rights, and the IP system. The term itself has no agreed international legal definition (WIPO 2001). TK on human health, wellness, and healing otherwise may be called traditional medical knowledge (TMK). Traditional medicine systems may be categorized as (i) Codified systems (disclosed in writing in ancient scriptures and are fully in the public domain) including the TMC, Ayurvedic, Siddha, and Unani systems of medicine; (ii) Non-codified traditional medicinal knowledge (not fixed in writing and undisclosed by TK holders) is passed on in oral traditions from generation to generation.

The high prevalence of traditional medicines throughout the world, coupled with efforts to integrate traditional medicines in modern national health systems, has increased the demand for information on the safety, efficacy, and quality of these medicines. The regulation of traditional medicines takes many different forms around the world. Depending on the national legislative and regulatory framework, they can be sold as prescription or non-prescription medicines, dietary supplements, health foods or functional foods. Over 120 WHO member states regulate herbal medicines the WHO has published key global technical guidelines, in terms of their quality, safety and efficacy, and sustainable use of herbal medicine. Several other sets of guidelines including the assessment of herbal medicines, the methodology for research and evaluation of traditional medicine, good manufacturing practices (GMPs) for herbal medicines, conservation and sustainable use of medicinal plants (good agricultural and collection practices—GACP) for medicinal plants are developing.

The use of genetic resources (GR) and associated TK is primarily regulated by the Convention on Biological Diversity (CBD) and the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization to the Convention on Biological Diversity (Nagoya Protocol). National biodiversity policies frequently reference traditional medicines and medical research. Many other national policies seek to create medical R&D programmes on the basis of their heritage of GR and associated TK. The essential effect of the CBD and the Nagoya Protocol is to confirm national sovereignty over GR and to establish a right of prior informed consent (PIC), approval, and involvement, over the access to, and use of, associated TK. Many of the issues highlighted in this debate concern genetic materials used as the basis for medical research, and traditional medical knowledge that is either used directly to produce new products or is used as a lead in researching new treatments. The principal shift in focus has been to recognize that: (i) the custodians and practitioners of traditional medical knowledge may have legitimate rights; (ii) their knowledge cannot be assumed to be in the public domain, free for anyone to use; and (iii) as financial and non-financial benefits from R&D are shared along the product development pipeline, an equitable portion should also be provided to the origin or source of the

material used in research. The Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) has called for benefits derived from TK to be shared with the respective communities (WHO 2006).

Concerns about improving patent examination in the TK area, in order to avoid erroneous patents on traditional medicines in particular, have led to initiatives at international and national levels. A leading example is the Traditional Knowledge Digital Library (TKDL), a collaborative project in India between the Council of Scientific and Industrial Research (CSIR), the Ministry of Science and Technology, and the Ministry of Health and Family Welfare. An interdisciplinary team of Indian medicine experts, patent examiners, information technology experts, scientists, and technical officers have created a digitized system enabling consultation of existing literature in the public domain relating to Ayurveda, Unani, Siddha, and Yoga. Such literature is generally available in traditional languages and formats. The TKDL therefore provides information on traditional medical knowledge in five international languages and formats which are understandable by patent examiners at international patent offices. The aim is to prevent the grant of erroneous patents while at the same time not newly publishing TK in a way that would facilitate its misappropriation.

The protection of traditional knowledge, including traditional medical knowledge, arises under Article 8(j) of the Convention on Biological Diversity. The issues surrounding the protection of traditional knowledge generally, and the implementation of Article 8(j) of the CBD specifically, have been extensively discussed in WIPO, in the context of the Convention on Biological Diversity, by the Secretariat of the WTO, and by the United Nations Conference on Trade and Development. The discussion continues in WIPO through the newly established.

Intergovernmental Committee on Intellectual Property and Traditional Knowledge, Genetic Resources, and Folklore, which meets for the first time April 30 to May 2, 2001. Moreover, several WTO Members have submitted documents to the Committee on Trade and Environment and/or the Council for Trade-Related Aspects of Intellectual Property Rights relating to the protection of traditional knowledge (WTO 2003). Further, some of the communications received by the General Council of the WTO from WTO Members in connection with preparations for the 1999 WTO Seattle Ministerial Conference dealt with the protection of traditional knowledge.

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