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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