Chapter 8
Phytochemistry, Pharmacology and Toxicity of Medicinal Plants

Lubna Tariq, Basharat Ahmad Bhat, Syed Suhail Hamdani, and Rakeeb Ahmad Mir

8.1 Introduction

Medicinal plants are known as the primary source of nourishment and natural metabolites for sound health maintenance (Mazzei et al. 2018). These are also called natural substances with a large number of pharmacological activities (Mishra et al. 2018b; Salehi et al. 2020) that are indispensable. After its invention, medicinal plants and herbal medicines have been used to treat different forms of acute and chronic diseases (Mishra et al. 2018a, b; Oladeji et al. 2020; Salehi et al. 2018b). Phytochemicals are bioactive, naturally present chemical compounds found in plants that provide health benefits for humans beyond those related to macronutrients and micronutrients (Hasler and Blumberg 1999; Septembre-Malaterre et al. 2018). These are the compounds which are responsible for the plant's flavor, aroma, and color and also contribute to the protection of plant from diseases and damage. Generally, these chemicals protect cells of plants from various environmental factors like drought, pollution, stress, pathogenic attack, and UV exposure (Gibson et al. 1998; Mathai 2000). More than 4000 phytochemicals have been characterized based on their physical and chemical characteristics and protective functions (Chae 2016; Meagher and Thomson 1999). Accumulation of phytochemicals occurs in different parts of plants such as stem, leaves, roots, fruits, flowers, or seeds (Chanda and Ramachandra 2019; Costa et al. 1999). Dietary phytochemicals in plants are found within the legumes, nuts, vegetables, seeds, fruits, herbs, spices, and fungi (Mathai 2000; Nahar et al. 2019). Some common sources include tomatoes, garlic, carrots, broccoli, grapes, cabbage, cherries, raspberries, strawberries, legumes, soy

L. Tariq · R. A. Mir (✉)
Department of Biotechnology, Baba Ghulam Shah Badshah University, Rajouri, India

B. A. Bhat · S. S. Hamdani
Department of Bioresources, University of Kashmir, Jammu and Kashmir, India

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food, and whole wheat bread (Moorachian 2000). Phytochemicals are known as secondary metabolites as they have many bioactive properties like antimicrobial effect, antioxidant activity, immune system stimulation, hormone metabolism modulation, and anticancer property, a decrease of platelet aggregation, and modulation of detoxification enzymes. It is well-known that plants produce these chemicals to protect themselves, but recent researches demonstrate that many phytochemicals can also protect human against diseases (Rao 2003), such as fatty acids, saponins, tannins, alkaloids, cardiac glycosides, and terpenoids (Iboroma et al. 2018; Melnyk et al. 2018; Shah et al. 2014). Medicinal plants have their unique characteristic properties against various diseases. Some of the phytochemicals in medicinal plants and their roles are illustrated in Table 8.1.

The physiologic properties of relatively few phytochemicals are well understood, and a lot of medicinal plants are under investigation to unravel their possible role in preventing or treating cancer and heart disease (Mathai 2000; Nahar et al. 2019). Phytochemicals have also been promoted for the prevention and treatment of diabetes, high blood pressure, and muscular degeneration (Chae 2016).

Table 8.1 Bioactive phytochemicals in medicinal plants

S. No	Class	Pharmacological activities	Characteristics	Uses	References
1.	Phenols	Antimicrobial, antiseptic, antitumor, anti-inflammatory,	Hydroxyl group directly attached to an aromatic ring, weakly acidic	Disinfection	Okwu (2005); Urquiaga and Leighton (2000)
2.	Tannins	Soothing relief, regenerates skin, anti-inflammatory, diuretics	Unpleasant taste, tans leather	In the production of leather and ink; in treating varicose ulcers, wounds, burns, and hemorrhoids, frostbite	Okwu and Okwu (2004)
3.	Flavonoids	Antioxidant, anti-carcinogens, antimicrobial, antitumor	Water-soluble, super antioxidant, and free radical scavenger	In prevention of oxidative cell damage, allergies, free radicals, microbes	Kandaswami et al. (1991); Manikandan et al. (2006)
4.	Alkaloids	Analgesic, anti-spasmodic, bactericidal effect	Bitter taste, colorless, nitrogen-containing bases, crystalline or liquid at room temperature	Raw material for the synthesis of useful drugs	Harbon (1998); Okwu and Okwu (2004); Stary (1991)
5.	Saponins	Expectorant, cough suppressant, hemolytic activity	Bitter taste, foaming property, hemolytic effect on red blood cells	Emulsifying agent	Okwu (2005); Oludare and Bamidele (2015)

8.2 Types of Phytochemicals

Depending upon the role in the metabolism of plants, phytochemicals are classified as primary or secondary. Common sugars, proteins, amino acids, pyrimidines and purines of nucleic acids, chlorophylls, etc. are classified under primary constituents, while the remaining chemical compounds like flavonoids, alkaloids, terpenes, plant steroids, lignans, saponins, phenolics, curcumin, and glucosides are classified as secondary constituents (Hahn 1998) (Table 8.2).

8.2.1 Phenolics

These are the largest category of a hydroxyl group (-OH) containing a class of phytochemicals that are ubiquitously distributed in plants (Walton et al. 2003). The three important dietary phenolics include phenolic acids, flavonoids, and polyphenols. The simplest natural class of this group is phenol (C_6H_5OH), whose hydroxyl group (-OH) is directly bonded to an aromatic hydrocarbon group.

Table 8.2 Common medicinal plants, part used, pharmacological action, and disease cured

S. No.	Plant	Part used	Action	Disease cured	References
01	*Zingiber officinale*	Rhizome	Carminative, anthelmintic emollient Laxative, expectorant	Anorexia, asthma, inflammations, vomiting flatulence, cough, nausea	Sofowora (1993)
02	*Carica papaya L.*	Fruits, leaves, latex	Appetizer, antifungal, anthelmintic, febrifuge, anti-inflammatory	Anorexia, fever, skin diseases intestinal worms, inflammations	Gill (1992)
03	*Allium sativum L.*	Bulbs	Expectorant, anti-inflammatory, antibacterial	Asthma, cough, bronchitis, nasal instillation	Gill (1992)
04	*Azadirachta indica*	Seed, bark, flowers, leaves	Anthelmintic, astringent, antiseptic, febrifuge, insecticidal, expectorant	Intestinal worms, skin diseases, malarial fever	Ade-Serrano (1982); Iwu (1993)
05	*Bridelia ferruginea Benth*	Root, stem, bark, leaves	Diuretic and hypoglycemic activity	Feverish pains, diabetes mellitus	Iwu (1993)
06	*Cymbopogon citratus*	Whole plant	Antiseptic, stomachic insecticide against mosquitoes, antifebrile, or as a deodorant	Vomiting, cold, eczema, fever	Gill (1992); Sofowora (1993)

Numerous beneficial properties to humans are exhibited by these phenolic compounds, and its antioxidant property plays an important role in the protection against free radicals like ROS. These compounds are important for the plants' color, growth, and reproduction and also act like defense mechanisms against parasites, predators, and pathogens (Báidez et al. 2007). Studies have shown that phenolic compounds exhibit potent antioxidant, anti-carcinogenic/anti-mutagenic, antibacterial, anti-atherosclerotic, anti-inflammatory, and antiviral activities to a lesser or greater extent (Han et al. 2007; Owen et al. 2000; Veeriah et al. 2006) (21–24), e.g., apples possess certain phenolic compounds which are linked to inhibiting the in vitro colon cancer (Veeriah et al. 2006). Several tested medicinal herbs and dietary plants have reported hundreds of natural phenolic compounds, especially phenolic acids, stilbenes, quinines, flavonoids, tannins, coumarins, curcuminoids, lignans, and other phenolic mixtures.

8.2.2 Phenolic Acids

Phenolic acids are a significant class of phenolic compounds that occur widely in the plant kingdom (Cai et al. 2004). Predominant phenolic acids include hydroxyl benzoic acids (e.g., protocatechuic acid, gallic acid, vanillic acid, syringic acid, and p-hydroxybenzoic acid) and hydroxycinnamic acids (e.g., p-coumaric acid, ferulic acid, chlorogenic acid, caffeic acid, and sinapic acid) (Cai et al. 2006). In medicinal herbs, gallic acid is widely present such as in *Cassia auriculata*, *Barringtonia racemosa*, *Cornus officinalis*, *Punica granatum*, *Polygonum aviculare*, *Rheum officinale*, *Rhus chinensis*, *Terminalia chebula*, and *Sanguisorba officinalis* as well as in dietary spices, for example, clove and thyme (Cai et al. 2003, 2006; Shan et al. 2005; Surveswaran et al. 2007). Hydroxybenzoic acids are also widely distributed in dietary plants and medicinal herbs. Plants like *Feronia elephantum*, *Paeonia lactiflora*, and *Dolichos biflorus* contain hydroxybenzoic acid; vanillic acid is found in plants like *Picrorhiza scrophulariiflora*, *Foeniculum vulgare*, and *Ipomoea turpethum*, while sugarcane straw and *Ceratostigma willmottianum* have syringic acid (Sampietro and Vattuone 2006; Stagos et al. 2006). The water-soluble salvianolic acid B is the major phenolic acid extracted from *Radix salviae miltiorrhizae.* This has been used for thousand years in China as a common clinically herbal medicine in terms of antioxidant agent. Phenolic acids play a key role in the reduction of lipid levels and blood cholesterol, in enhancing bile secretion, and in antimicrobial activity against strains of some bacteria like *Staphylococcus aureus* (Gryglewski et al. 1987). Phenolic acids also possess some diverse bioactivities such as anti-inflammatory, anti-ulcer, anti-spasmodic, anti-depressant, cytotoxic, and antitumor (Ghasemzadeh et al. 2010).

8.2.3 Flavonoids

Flavonoids are a class of compounds extensively present in nature. Concerns over their substantial profitable biologically active benefits, including antiviral/antibacterial, cardioprotective, anti-inflammatory, antidiabetic, anti-aging, and anticancer, have been received for a long time and have been well supported by various research findings (Krych and Gebicka 2013; Ragab et al. 2014; Tian et al. 2014). These compounds usually have the basic skeleton of the structure of phenyl benzopyrone (C6-C3-C6) composed of two aromatic rings (A and B rings) bound by three carbons normally in an oxygenated central pyran ring, or C ring (Cai et al. 2004). These polyphenolic compounds are widely distributed in nature. Flavonoids have been reported to play a major role in effective ancient medical therapies, and their use has continued to this day. In vascular plants, flavonoids are ubiquitous and exist as glucosides, glycones, and methylated derivatives. Recent attention has been paid to flavonoids due to their diverse pharmacological and biological activity. Flavonoid compounds have been reported to exercise several biological properties including anti-microbial, anti-inflammatory, cytotoxic, and antitumor activity, but the best described property of almost any group of flavonoids is their ability to function as strong antioxidants. Various forms of flavonoids are present in almost all dietary plants, such as fruits and vegetables, and previous reports indicate that flavonoids are the largest class of phenolics in the herbs and dietary spices tested (Cai et al. 2004; Huang and Xing 2007; Shah et al. 2014; Surveswaran et al. 2007). Different categories of flavonoids from medicinal herbs and dietary plants include hesperetin, naringenin, taxifolin, quercetin, luteolin, baicalein, apigenin, kaempferol, chrysin, catechin, myricetin, taxifolin, morin, galangin, glycitein, eriodictyol, catechin, epigallocatechin, silymarin, and epicatechin. Glycosides such as vitexin, apigetrin, and baicalin are mainly found in Labiatae, Asteraceae, inflorescences of *Chrysanthemum morifolium*, aerial parts of *Artemisia annua*, and roots of *Scutellaria baicalensis.* Flavonoids constitute a wide range of substances that play an important role in protecting biological systems against the harmful effects of oxidative processes on macromolecules, such as carbohydrates, proteins, lipids, and DNA (Atmani et al. 2009).

8.2.4 Tannins

Tannins are a high molecular weight heterogeneous group of polyphenolic compounds. They have capacity to develop reversible and irreversible complexes with mostly proteins, alkaloids, minerals, polysaccharides (cellulose, pectin, hemicellulose, etc.), nucleic acids, etc. (Licitra et al. 1996; Mueller-Harvey and McAllan 1992; Schofield et al. 2001). These compounds are classified into two classes: condensed tannins (proanthocyanidins) and hydrolysable tannins (gallo- and ellagitannins. Among culinary plants and medicinal herbs, tannins are a wide class of polyphenolics. Oligomeric proanthocyanidins, widely found in pine bark and skin and grape seed, are deemed to be the most effective antioxidants and are commonly used in the health care and treatment of cancer (Huh et al. 2004). Among 126 medicinal herbs in India, 10 have high levels of hydrolyzable tannins (Surveswaran et al. 2007). In *Euphorbia hirta*, *Rhus succedanea*, and *Glycyrrhiza glabra*, some gallotannins were found. Several ellagitannins such as corilagin and casuarictin have been extracted from fruits like *Chebula* and *P. granatum* peels. *Areca catechu* and *Camellia sinensis* also contain tannins named leucoanthocyanidins and proanthocyanidins, respectively. Many plant species synthesize both condensed and hydrolyzable tannins, e.g., *S. officinalis*, *P. granatum*, *Acacia catechu*, *Rosa chinensis*, etc. (Cai et al. 2004; Schofield et al. 2001; Surveswaran et al. 2007). The tannin-containing plant extracts are being used as astringents against diuretics, diarrhea, duodenal, and stomach tumors (De Bruyne et al. 1999), as well as antioxidant, anti-inflammatory, homeostatic, and antiseptic drugs in Asia (Japan and China) (Dolara et al. 2005).

8.2.5 Alkaloids

Alkaloid term is derived from the word “alkaline,” and these are thus natural products with heterocyclic nitrogen atoms. The nature of the alkaloids is basic and is naturally synthesized in plants, animals, fungi, and bacteria. These are often optically active but are usually colorless and bitter. Quinine, one among the alkaloids, is the bitterest substance (Mishra 1989). Alkaloids feature one of the most effective and important therapeutic plant substances (Okwu 2005). Alkaloids are important for plant protection and survival because they ensure their safety against insects, microorganisms via antibacterial and antifungal activity, and herbivores (feeding deterrents), as well as other plants by means of allelopathically active chemicals (Molyneux et al. 1996). Some examples of alkaloids are morphine, nicotine, codeine (*Papaver somniferum*), reserpine (*Rauwolfia vomitoria*), cocaine, and quinine (*Cinchona succirubra*). The presence of alkaloids within plants gives plant some specific characteristics with respect to their medicinal values such as therapeutic potential including antiarrhythmic effects (quinidine, spareien), antihypertensive effects (indole alkaloids), anticancer action (dimeric vincristine, indoles, vinblastine), and anti-malarial activity (quinine). These are just a few examples which illustrate the tremendous importance of this plant constituent group (Wink et al. 1998). Synthesis of alkaloids is the characteristic of all organs of a plant. Pure, isolated plant alkaloids and related synthetic derivatives are used as essential therapeutic agents for their anti-spasmodic, analgesic, and bactericidal effects (Stary 1991). When administered to animals, they demonstrate marked physiological activity (Okwu and Okwu 2004). Besides, alkaloids are also poisonous to humans, and others have drastic physiological processes, which is why they are commonly used in medicine to produce medicines. Quinine extracted from the cinchona tree bark (*C. succirubra*) is exceedingly valuable for the treatment of malaria (Rao et al. 1978).

8.2.6 Saponins

Saponins are glycosides of both triterpenes and steroids distinguished by their bitter or astringent flavor, foaming properties, hemolytic effects on red blood cells, and binding properties to cholesterol (Okwu 2005). Saponins have been shown to have beneficial (lowering cholesterol) and deleterious (cytotoxic and intestinal epithelium permeabilization) effects and to exhibit biological activity dependent on structure. It is also used in medicine as an expectorant and an emulsifying agent (Harbon 1998).

8.3 Pharmacological Activities

According to the World Health Organization, over 80% of the world's population, or 4.3 billion people, rely upon traditional plant-based systems of medicine to provide them with primary health care (Bharti et al. 2018). Medicinal plants play a vital role in the development of new drugs. Many plant-based new drugs, including deserpidine, lectinan, plaunotol, Z-guggulsterone, nabilone, rescinnamine, E-guggulsterone, reserpine, teniposide, vinblastine, etoposide, vincristine, ginkgolides, and artemisinin that are extracted from higher plants, were introduced in the US drug market between 1950 and 1990. From 1991 to 1995, further 2% of the new drugs were introduced such as irinotecan, topotecan, paciltaxel, gomishin, etc. Several pharmacological activities including the treatment of cancer, immune-modulation, nervous system activation, antipyretic, analgesic, hepatoprotection, antidiabetic nature, etc. have been possessed by plants and their products (González-Stuart et al. 2014). Scientists have even started correlating phytochemical constituents of a plant with its pharmacological activity as well as the botanical properties of plants with their pharmacological activity (Heinrich et al. 2020; Nahar et al. 2019). Medicinal plants are being used as treatments for human diseases, as they contain pharmaceutical benefit components. The issue of microbial resistance is growing, and the prospects for potential use of antimicrobial drugs are still unclear (Lewis 2017). Therefore, plants have been a reliable source of natural products for the preservation of human health for a long time, with increasingly extensive natural therapy studies. Studies have revealed methanol extracts from bark and roots from several plants like *Sida cordifolia*, *Acacia nilotica*, *Tinospora cordifolia*, *Ziziphus mauritiana*, and *Withania somnifera* possess substantial antibacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis*, *Xanthomonas axonopodis*, and *Pseudomonas fluorescens* and antifungal activity against *Drechslera turcica*, *Fusarium verticillioides* (Harit et al. 2013), and *Aspergillus flavus*. Among these leaf extracts, the highest antibacterial activity against *B. subtilis* is shown by *S. cordifolia* and *A. nilotica*. Bark and leaf extracts of *A. nilotica* show important antifungal activity against *Z. mauritiana* and *A. flavus*, while *T. cordifolia* posses significant antifungal activity against *D. turcica*.

Studies done on aqueous and ethanol extracts of *A. paniculata* for investigating antibacterial activity against nine species of bacteria named *Shigella sonnei*, *Salmonella typhimurium*, *Staphylococcus aureus*, *Escherichia coli*, *Bordetella pertussis*, *Pseudomonas aeruginosa*, *Legionella pneumophila*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes* showed positive results only for *B. pertussis* and *L. pneumophila* (Xu et al. 2006). *A. paniculata* show anti-diarrheal activity against *E. coli*-associated diarrhea (Gupta et al. 1990, 1993). Methanol extracts from *Murraya koenig* leaf possess antibacterial activity against *E. coli* and *S. typhi* (Singh and Sedha 2018). Aqueous and ethanol extract of *Garcinia kola*, *Xylopia aethiopica*, and *Cajanus cajan* were tested on *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans*, and *Pseudomonas aeruginosa*. All the results were positive for antibacterial activity, and ethanol extract was found to be more effective (Ezeifeka et al. 2004).

8.3.1 Anticancer

Cancer is the third leading health issue in both developing and developed countries, and one of the world"s leading causes of death. About 12.5% of the population died due to cancer, according to the WHO in 2004. Chemotherapy, radiotherapy, immunotherapy procedures, and surgery actually induce several adverse effects on non-target cells/tissues. This fuels the need for alternative cancer treatments and therapies (Akindele et al. 2015; Veerakumar et al. 2016). Numerous cancer research studies are going on using traditional medicinal plants in an attempt to discover new therapeutic agents lacking the toxic side effects associated with the current chemotherapeutic agents (Hartwell 1982). Herbal plants/medicines have been shown to cause less side effects in cancer cure over the past decades and have been well-accepted worldwide at (Akerele et al. 1991; Hartwell 1982). Natural active components such as phenol and flavonoids that exist in medicinal plants protect toward harmful effects within biological systems. They were tested for their antitumor, proapoptotic, and anti-angiogenic effects (Carocho and CFR Ferreira 2013; Ghasemzadeh and Ghasemzadeh 2011).

Historically, secondary plant metabolite derives constituents of anticancer such as vinblastine, vincristine, camptothecin, flavopiridol, podophyllotoxin, silvestrol, etc. that are used worldwide (Batra & Sharma, 2013). *Cedrus deodara* contains a standardized lignin AP9-cd that is known to show the cytotoxicity in various cell lines of human cancer. Saponins dasyscyphin C isolated from leaves of *Eclipta prostrata* and gymnemagenol isolated from *Gymnema sylvestre* have shown anticancer activity after being tested on HeLa cells. *Catharanthus roseus*, vinca alkaloids, vincristine, and vinblastine were the first drugs to progress into clinical use for cancer treatment. These are mainly used for treating a range of cancers, including lymphomas, leukemias, breast cancer, advanced testicular cancer, lung cancers, and Kaposi's sarcoma, in conjunction with other cancer chemotherapeutic medications. Besides roscovitine, a synthetic agent derived from olomoucine, a natural product, extracted from *Raphanus sativus*, also shows anticancer activity (Cragg et al. 2011; Meijer and Raymond 2003). Silymarin has also prevented skin carcinogenesis caused by benzoyl peroxide due to its chemoprotective action (Agarwal et al. 1994; Kohno et al. 2002; Lahiri-Chatterjee et al. 1999).

8.3.2 Antidiabetic

Diabetes mellitus (DM) is a severe, acute, and complicated metabolic disorder with various etiologies with significant, both acute and chronic, consequences (Soumya and Srilatha 2011). It is estimated that this disease affects 25 percent of the world population (Arumugam et al. 2013). The quest for newer antidiabetic drugs from the natural source continues (Wadkar et al. 2008) due to the many drawbacks associated with the use of current synthetic antidiabetic drugs. Natural products, especially of plant origin, are the key quarry for the discovery of potential lead candidates and play an indispensable role in future drug development programs (Salehi et al. 2018a; Sharifi-Rad et al. 2018a, b). In addition, many plants provide a rich source of bioactive chemicals free from unwanted side effects and have effective pharmacological activities (Abdolshahi et al. 2018; Mishra et al. 2018a, b; Sharifi-Rad et al. 2018a, b; Singab et al. 2014). Most plants were considered as fundamental source of potent antidiabetic drugs for centuries. Across developing countries in particular, medicinal plants are used to treat diabetes, in order to alleviate the pressure on the population of the cost of traditional medicines (Bahmani et al. 2014). Nowadays it is advised to treat diseases like diabetes using medicinal plants (Kooti et al. 2015), since these plants incorporate different phytoconstituents such as flavonoids, saponins, terpenoids, carotenoids, glycosides, and alkaloids that may have antidiabetic activity (Afrisham et al. 2015). Ríos et al. (Ríos et al. 2015) identified medicinal plants such as bitter melon, aloe, caper, cinnamon, banaba, cocoa, fenugreek, coffee, garlic, gymnema, guava, nettle, soybean, green and black tea, sage, turmeric, yerba mate, and walnut used as antidiabetic agents for the treatment of diabetes and its comorbidity. The mechanisms of natural products, with attention to compounds of high interest such as *Artemisia* with 13 species, fukugetin, *Ficus* with 18 species, *Terminalia* with 11 species, *Euphorbia* with 10 species, and Solanum with 12 species, are some of the genera with a large number of antidiabetic species. Studies have shown that in rabbits hyperglycemia caused via oral administration of glucose was significantly cured by water extracts of *A. paniculata* (Borhanuddin et al. 1994). Pterostilbene and marsupin (important phenolic constituents of the *Pterocarpus marsupium* heartwood) significantly decreased blood glucose levels in streptozotocin-induced diabetic rats, and the results were comparable to metformin (Rizvi et al. 1995). Piperine is a naturally occurring alkaloid in fruit of *Piper* species. With metformin, it has bioenhancing effects in reducing blood glucose levels (Atal et al. 2016; Rizvi et al. 1995). *Camellia sinensis* is also known for significantly reducing the blood glucose level in streptozotocin-induced diabetic rats (Al-Attar and Zari 2010). *Phyllanthus amarus* is also found to have hypoglycemic effects (Adedapo and Ofuegbe 2014).

8.3.3 Antipyretic Activity

Medicinal plants possess this pharmacological activity in a number of plants. Plants used as an antipyretic agent help by lowering body temperature from an elevated state to prevent or reduce fever. An antipyretic is a form of medication that prevents or decreases fever by rising body temperature from an elevated state. Antipyretic activity of polyherbal formulation consisting of *Adhathoda vasica*, *Moringa oleifera*, and *Andrographis paniculata* named JU-RU-01 was assessed in Wistar rats having Brewer's yeast-induced pyrexia (Chandra et al. 2010). In rat models the methanol extract of *Rhynchosia cana* and *Nelumbo nucifera* also exhibited antipyretic influence (Mukherjee et al. 1996; Vimala et al. 1997). Chloroform and alcoholic extracts of the leaves of *Hygrophila spinosa* demonstrated potent antipyretic and anti-inflammatory activity in a dose-dependent manner (Patra et al. 2009).

8.3.4 Anti-Allergic Activity

The allergy refers to our immune systems' overreaction in response to body interaction with the kind of foreign substances. This is exacerbated since the body typically treats these foreign substances as harmless and no reaction occurs in non-allergic individuals. Together with prescription medications, herbal medicines are also in demand because of their reduced side effects as anti-allergens. *Vitex negundo* ethanol extract has been found to inhibit the immunologically mediated degranulation of mast cells effectively than that of the 40/80 compounds (Nair et al. 1995). Alcoholic extract of the *Andrographis paniculata* and *Nyctanthes arbor-tristis* plants, hexane-soluble extract of the *Cedrus deodara* wood, and aqueous extract of the *Albizia lebbeck* bark were found to have important anti-allergic activity when examined in rats of experimental anaphylaxis and mast cell degranulation models (Al Rashid et al. 2019).

8.3.5 Antioxidant

Oxygen is a highly reactive atom that can become a part of potentially destructive molecules commonly referred to as free radicals such as reactive oxygen species (ROS). We significantly exceed the ability of the endogenous cellular antioxidant defense system when ROS is present at certain levels and thus case oxidative stress. The resulting damage to the cells and organs will cause disease processes and/or accelerate them. Several degenerative conditions such as coronary heart disease, atherosclerosis, cancer, and aging involve oxidative stress (Finkel and Holbrook 2000; Song et al. 2010; Valko et al. 2007). The free radicals will invade the body's healthy cells, causing them to lose their function and structure. Antioxidants are able to regulate or deactivate free radicals before damaging cells. Antioxidants are necessary to maintain optimum cellular and systemic health (Halliwell 1994). Natural antioxidants are not commonly used today, because of their small sources and high price. In the food industry, synthetic antioxidants such as butylated hydroxyanisole and butylated hydroxyltoluene are commonly used. There is, however, the consensus that synthetic antioxidants should be substituted with natural antioxidants because certain synthetic antioxidants have demonstrated health hazards and toxicity, most prominently carcinogenic effects (Ito et al. 1986; Safer and Al-Nughamish 1999). The best outcomes in health and nutrition can be obtained not only through the intake of high antioxidant quality fruits and vegetables but also from medicinal plants and herbs (Jastrzebski et al. 2007). Numerous studies have indicated that some medicinal plants have more powerful antioxidant activity than vegetables and fruits, and phenolic compounds have been a major contributor to these plants' antioxidant activity (Cai et al. 2004; Dragland et al. 2003). Some plants having the highest antioxidant activity are *Eriobotrya japonica*, *Dioscorea bulbifera*, *Ephedra sinica*, and *Tussilago farfara*, while some plants possess higher radical scavenging activity rather than an antioxidant activity, e.g., *Arctium lappa* and *Fritillaria verticillata.* It has been proved by various studies the total phenolic content and antioxidant capacity of a medicinal plant are linearly correlated with each other, but exceptions are also there, e.g., *Perilla frutescens*, displaying relatively high antioxidant potential but not having comparable phenolic concentration (Singleton and Rossi 1965).

8.4 Toxicity of Medicinal Plants

The use of plants for therapeutic purposes is becoming ever more popular as they are thought to be effective and free of side effects. However, the justification for using medicinal plants has largely rested on long-term clinical observation with little or no scientific data about their effectiveness and safety (Zhu et al. 2002). Medicinal herbs are used as a medicine based on the ancient folk use perpetuated over several generations. A thorough scientific investigation of these plants is imperative with the rise in the use of herbal medicines, based on the need to validate their folkloric usage (Abdullahi 2011). Herbs should be safe, but there have been reports of many insecure and fatal side effects (Izzo 2004; Whitton et al. 2003). Phytotherapeutic products are often considered less toxic, mistakenly because they are "natural" (Gesler 1992). However, those products contain biologically active principles that could lead to adverse effects (Bent and Ko 2004). Following exposure to the highly toxic material, an adverse effect is characterized as an irregular, unexpected, or harmful change. The serious effects of toxicity could be allergic reactions, the abnormal weight of organs and body, altered levels, and activities of enzymes (Duffus et al. 2009), while in some cases death could be the most serious effect. Thus, the same methods used for new synthetic drugs must submit all "natural" products used in therapeutics to the efficacy and safety tests (Talalay and Talalay 2001). Toxicology studies are important before determination of any appropriate dosage of drug. Clearly, the lungs are essential for all airborne compounds, while the significant site for absorption is rarely the skin (Deshpande 2002). These are also important in explaining drug toxicity profiles.

Toxicity depends not only upon the substance's dosage but also upon the substance's toxic properties. In the evaluation of therapeutic dose in pharmacology and herbalism, the relationship between these two factors is significant. The critical preclinical necessary information includes a 2-week toxicity testing in sensitive species (usually rodents) plus toxicokinetics which should allow the no-observed level of adverse effect (NOAEL) to be determined. In general, the NOAEL is based on studies of animal toxicity. For setting exposure limits, the NOAEL is essential. The acceptable daily intake (ADI), for example, is based on the NOAEL. This is a measure used to assess the appropriate intake for food additives and pollutants such as pesticides and veterinary drug residues and thus to assess the level of protection in food (Chae 2016; Renwick 1990). Different toxicity levels which are checked are mentioned as under:

8.4.1 Acute Toxicity

Acute toxicity is characterized as the toxic effects produced by single drug exposure by any route over a short period. Animal acute toxicity trials are deemed appropriate for any medication intended for human use. The main aim of acute toxicity studies is to identify a single dose that causes major adverse effects or life-threatening toxicity, often involving an estimate of the minimum dose that causes lethality. This is the only type of study in the pharmaceutical drug development where lethality or life-threatening toxicity is an endpoint as documented in current regulatory guidelines (Attah et al. 2019a; b). Different routes may be used to assess the toxicity of a compound in animals, but two most commonly used modes of animal studies are through intraperitoneal infusion or oral route (Poole and Leslie 1989). The acute study offers guidelines for the selection of doses for the sub-acute and chronic low-dose study, which might be more clinically important (Hasumura et al. 2004; Janbaz et al. 2002).

8.4.2 Sub-Acute Toxicity

Repeated doses of the drugs are given in sublethal amounts for duration of 14-21 days in sub-acute toxicity studies. Sub-acute studies of toxicity are being used to evaluate the effect of the drug on blood biochemical and hematological parameters and to determine histopathological changes (Baki et al. 2007).

8.4.3 Chronic Toxicity

For chronic toxicity research, to evaluate the carcinogenic and mutagenic potential of drug, medication is given at various doses over duration of 90 days to over a year. The criteria used in chronic toxicity studies are the same as those used in sub-acute studies. Multiple-dose trials are required to ensure natural products are safe. Clinical observations of acute assays, on the other hand, are valuable tools for defining the doses to be tested in multiple-dose experiments, together with pharmacological studies in humans and animals (Alvarez et al. 2004; Tagliati et al. 2008).

8.5 Importance of Different Parameters in Toxicity Studies

A summary of ethno-medicinal uses, toxicity study, and its safety level of different medicinal plants is given in Table 8.3.

8.5.1 Gross Behavior Assessment

The assessment of gross behavior generally in mice can be evaluated using the Morpurgo model (Morpurgo 1971). CNS depression (hypoactivity, exitus, passivity, ataxia, relaxation narcosis, ptosis), ANS effect (hyperactivity, exophthalmia, stereotypy, irritability), and CNS stimulus parameters (Straub tail, analgesia, convulsions tremors) and other parameters are specific parameters measured for gross behavior studies.

8.5.2 Body Weight

Changes in body weight are markers of adverse side effects, since surviving animals cannot lose more than 10% of the initial body weight (Teo et al. 2003). The hematopoietic system is one of the most responsive targets for toxic compounds and an important index of human and animal physiological and pathological status (Mukinda and Syce 2007). The different hematological parameters investigated in this study are valuable indices for evaluating plant extract toxicity in animals (Yakubu et al. 2008).

Table 8.3 List of medicinal plants, their family, ethno-medicinal uses, toxicity study, and its safety level

S. No.	Plant (family)	Pharmacological activity	Toxicity study	Result	References
1.	*Acacia karroo* Hayne (Fabaceae)	Gum is an important food source	Acute, sub-acute	Toxic	Adedapo et al. (2008)
2.	*Acmela brasiliensis* DC (Asteraceae)	Respiratory infections and pain	Acute, sub-acute	Less toxic	Burger et al. (2005)
3.	*Aconitum napellus* Linn. (Ranunculaceae)	Pain, coldness, vertigo, and general fatigue	Chronic	Safe	Wada et al. (2006)
4.	*Aframomum melegueta (Roscoe)* K. Schum. (Zingiberaceae)	Stomachache, diarrhea, and snakebite	Sub-chronic	Toxic (liver)	Ilic et al. (2010)
5.	*Artemisia afra (Jacq. Ex. Willd)* (Asteraceae)	Cough, colds, sore throat, heart burns, hemorrhoids, fever, malaria, asthma, and diabetes mellitus	Acute, chronic	Safe	Mukinda and Syce (2007)
6.	*Asparagus pubescens* Bak (Liliaceae)	Used as remedy for liver and kidney disorders	Acute	Safe	Nwafor et al. (2004); Taziebou et al. (2007)
7.	*Camellia sinensis (L.) Kuntze* (Theaceae)	Antioxidant, anti-allergic, antiangiogenic, anti-inflammatory, and hypolipidemic	Sub chronic	Safe up to 1.25%	Takami et al. (2008)
8.	*Calendula officinalis* L. (Asteraceae)	Anti-inflammatory, wound healing and antiviral	Acute, sub-acute	Safe	Silva et al. (2007)
9.	*Carica papaya* L. (Caricaceae)	Anti-fertility	Acute, sub-chronic	Safe	Lohiya et al. (2006)
10.	*Cassytha filiformis* R.Br. (Lauraceae)	Diabetes mellitus, ulcer, and cough	Sub-chronic	Safe	Babayi et al. (2007)
11.	*Centaurium erythraea (L.) Rafn.* (Gentianaceae)	Sedative, antipyretic, asthma, jaundice, intestinal parasitic infestation, rheumatism, wounds and sores, blood pressure, edema, and digestive disorders	Acute, sub-chronic	Safe	Tahraoui et al. (2010)
12.	*Euphorbia hirta* L. (Euphorbiaceae)	Inflammation, respiratory tract, and asthma	Repeated (14days)	Toxic	Adedapo et al. (2005)
13.	*Ficus exasperata (Vahl)* (Moraceae)	Stimulant, ring worm, and chest complications	Repeated (3 days)	Leaves were toxic while stems were safe	Irene and Iheanacho (2007)
14.	*Helicteres isora L.* (Sterculiaceae)	Diabetes mellitus, colic, gastropathy, diarrhea, and dysentery	Acute, repeated (28 days)	Safe	Kumar et al. (2007)

(continued)

Table 8.3 (continued)

S. No.	Plant (family)	Pharmacological activity	Toxicity study	Result	References
15.	*Ipomoea batatas* L. (Convolvulaceae)	Isolated compound ipomeamarone	Acute	Toxic for liver	Pandey (2008)
16.	*Salvia scutellarioides* Kunth (Lamiaceae)	Antihypertensive and diuretic properties	Acute, sub-acute	Safe	Ramírez et al. (2007)
17.	*Sida cordifolia* *L.* (Malvaceae)	Stomatitis of asthma and nasal congestion	Acute	Toxic at high dose	Franco et al. (2005)
18.	*Smilax kraussiana* (Liliaceae)	Inflammation	Acute	Safe up to 0.24 g/kg	Assam et al. (2010)
19.	*Polyalthia longifolia (Sonn.) Thw* (Annonacea)	Treatment of fever, skin disease, diabetes, hypertension	Acute	Safe	Chanda et al. (2012)
20.	*Ficus exasperata (Vahl)* (Moraceae)	Chest pain, eye troubles, and stomach pains and to arrest bleeding	Acute	Safe	Bafor and Igbinuwen (2009)
21.	*Garcinia hanburyi* Hook. f. (Guttiferae)	Cytotoxic and anticancer activity	Chronic	Safe	Qi et al. (2008)
22.	*Datura stramonium* L. (Solanaceae)	Asthma, gastric pain, anti-inflammatory, stimulation of central nervous system, and skin infection	Chronic	safe	Gidado et al. (2007)
23.	*Cucurbita maxima* Duch. (Cucurbitaceae)	Stomach pain, anti-inflammatory, and antipyretic	Acute, sub-acute	Safe	Cruz et al. (2006)
24.	*Cassia fistula* L. (Caesalpiniaceae)	Mild, pleasant purgative action, antifungal, antiviral, menstrual disorders, and fever	Acute, sub-chronic	Less toxic	Akanmu et al. (2004)
25.	*Zingiber zerumbet* Smith. (Zingiberaceae)	Anticancer and cytotoxic activity	Acute	Toxic at high dose	Ibrahim et al. (2010)
26.	*Bridelia ferruginea Benth* (Euphorbiaceae)	Diabetes	Acute, sub-chronic	Safe	Bakoma et al. (2013)
27.	*Vernonia amygdalina* Del (Compositae)	Antimalaria, anticancer, antimicrobial, as laxative herbs, and anthelmintic	Sub-acute	Safe	St Augustines (2009)
28.	*Tanacetum vulgare* L. (Asteraceae/ Compositae)	Menstrual irregularities, anthelmintic, carminative, antispasmodic, stimulant, and tonic properties	Acute, chronic	Safe	Lahlou et al. (2008)
29.	*Pongamia pinnata* (L.) Merr. (Papilionaceae)	Anticonvulsant, hypotensive effects, bronchitis, chronic fever, whooping cough, and skin diseases	Sub-acute	Safe	Baki et al. (2007)

(continued)

Table 8.3 (continued)

S. No.	Plant (family)	Pharmacological activity	Toxicity study	Result	References
30.	*Pothomorphe umbellata* L. Miq. (Piperaceae)	Liver and inflammation disorders	Acute, sub-chronic	Safe	Barros et al. (2005)

8.5.3 Organ Weight

Changes in organ weight have long been recognized as a sensitive measure of chemically induced changes in tissues, and in toxicological studies, a comparison of organ weights between control and treated groups was historically used to predict the toxic effect of a test substance (Nisha et al. 2009; Pfeiffer 1968). Organ weight is a swelling, atrophy, or hypertrophy index (Amresh et al. 2008). Body weight and internal organs such as the heart, liver, thymus glands kidney, spleen, etc. are toxicity indices that are simple and sensitive after exposure to toxic substance (Teo et al. 2003). Toxicity data are important to predict the safety of medicinal products before use (McNamara 1975).

8.5.4 Serum Biochemical Importance

When ingested, the body interacts with a herbal product in an attempt to get rid of any harmful toxins, especially if the body is unable to convert the foreign substance into cellular components. These insults are usually expressed by changes in enzyme levels and other components of the cells. The commonly involved enzymes are glutamate-oxaloacetate transaminase (AST/GOT), pyruvate transaminase (ALT / GPT), and alkaline phosphatase (ALP). Components such as urea and uric acid are also critical resources for toxicity (Maxwelll et al. 2007).

8.6 Conclusion and Future Prospectus

Medicinal herbs are considered the most basic and effective therapeutic approach since time immemorial and play a major role in the advancement of primary health care. All the pharmacological properties of the plants are mostly associated with the presence of secondary metabolites. According to the WHO, nearly 25% of current pharmaceutical products are derived plants. Many more are synthetic analogs based on plant-isolated prototype compounds. In India, approximately 70% of modern medicines are extracted from natural products. In the coming future, the basic uses of plants in medicine will continue as a source of bioactive and as basic raw material for the food, pharmacology, cosmetics, and perfume industries. It is extremely difficult to design or identify a phytochemical with a high specificity and functionality to act on a biological system. This is largely due to the presence of a large number of phytochemicals with similar chemical structures and physiological reaction complexities. While herbal drugs are considered to be the safest and most harmless therapeutic device, recent adverse effects reported from herbal use have significantly undermined its claims for protection or effectiveness, and also, most herbal plants are not well cited or documented. Herbal drug toxicological testing should promote and explain their validity and health. However, despite the number of phytochemicals isolated so far, nature still has a lot more in reserve. A lot more of these phytochemicals can be detected with the developments in synthetic biology and the development of more advanced isolation and analytical techniques. To further encourage research in this area, the proper use of technical innovations and a clear understanding of the formalized language and of traditional medicine also become a requirement.

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