Therapeutic Properties of Herbal Constituents Subjected for Clinical Trials

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1 Introduction

Nature is source of variety of medicinal products from the very ancient time, with numerous varieties of drugs useful for the mankind and directly produced from the plant sources. One particularly strong application of Penicillin's discovery, together with the fact that many medications come from microorganisms, etc. In the late 1980s, combinatorial chemistry diverted the focus of efforts of drug discovery directly from nature to the bench of laboratories, which was further subjected for clinical trials.

However, natural compounds also face several kinds of challenges in the discovery of new drugs, viz., barriers of technical screening, isolation of new compounds, and characterization and optimization of the same, which has directly contributed to rejection in their quest by the pharmacy industries since the early 1990s till now. Nowadays, several developments in the field of technology exist, which involves improvement in use of analytical tools, genome studies, and various engineering-oriented strategies, and advances in microbial culturing, etc., are opening up new opportunities in the field of research.

New drug discovery with the use of natural products is a very demanding task in the field of research for the designing of new compound leads. It provides description of the bioactive compounds originating from natural resources, analysis on the basis of presence of phytochemicals, and their categorization and investigation on

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the basis of therapeutic evidence, because this is the base with which any drug is subjected for clinical trials.

This chapter provides a brief description about some common natural products and also reviews clinical trials performed on these natural products. The possible mechanisms of action for the practical impact of the following natural compounds are also described.

1.1 Garlic

Garlic (*Allium sativum*) is an aromatic yearly herbaceous spice and one of the most seasoned and authenticated herbs that have been used since ancient times. It belongs to Amaryllidaceae family [1, 2]. Garlic is utilized as a remedy for numerous common maladies because of hundreds of phytochemicals present in it [2]. Reportedly it includes sulfur-containing compounds such as ajoenes (E-ajoene, Z-ajoene), thiosulfinates (allicin), vinyldithiins (2-vinyl-(4H)-1,3-dithiin; 3-vinyl-(4H)-1,2-dithiin), sulfides (diallyl disulfide [DADS], diallyl trisulfide [DATS]), and others, which account for 82% of the total garlic sulfur content [3].

Garlic has solid antioxidant properties due to its dietary and phenolic compounds. An orderly survey and meta-analysis of 12 randomized controlled trials (RCTs) uncovered noteworthy increments in serum antioxidant capacity and superoxide dismutase levels and diminished serum malondialdehyde levels as a result of garlic (*Allium sativum*) supplementation (80–4000 mg/day for 2–24 weeks) [2]. Garlic extract was found to increase the activities of some antioxidant enzymes (e.g., superoxide dismutase [SOD]) and decrease glutathione peroxidase (GSH-Px) in rat liver tissues. Notably, several reports indicated that aged garlic extract (AGE) rich in flavonoids, phenol, and different sulfur compounds, e.g., S-ally-(L)-cysteine (SAC), shows high radical scavenging activity [4]. Although experimental studies have shown a clear hypoglycemic effect of garlic, the effect of garlic on human blood glucose remains controversial. Garlic significantly lowered total cholesterol and low-density lipoprotein (LDL) cholesterol and moderately increased high-density lipoprotein (HDL) cholesterol compared to placebo in diabetic patients [5]. In a double-blind clinical trial ($N = 38$), a combination of nettle leaves (20% w/w), onion and garlic (20%), fenugreek seeds (20%), walnut leaves (20%), cinnamon bark (10%), and berry leaf (10%) powder effectively controlled type 2 diabetes in human subjects [6]. Aged garlic extract (2400 mg/day orally) reduced volumes of low attenuation but not total fibrous or fibro fatty plaque in the coronary arteries of patients with diabetes mellitus ($N = 80$) compared with placebo [7]. Crushed raw garlic (100 mg/kg twice daily for 4 weeks) reduced waist circumference, systolic and diastolic blood pressure, triglycerides, and fasting blood glucose, and increased serum HDL cholesterol in patients with metabolic syndrome [8]. In an open-label phase 1 trial, a combination of *A. sativum*, *Aloe vera*, *Nigella sativa*, *Plantago psyllium*, *Silybum marianum*, and *Trigonella foenum-graecum* reduced fasting blood

glucose, HbA1, LDL, and triglycerides in patients with hyperlipidemia and hyperglycemia with advanced type 2 diabetes [9].

Garlic and its preparations are widely known as agents for the prevention and treatment of cardiovascular diseases. Extensive scientific literature supports the suggestion that garlic consumption has significant effects on lowering blood pressure, preventing atherosclerosis, reducing cholesterol and triglycerides, inhibiting platelet aggregation, and increasing fibrinolytic activity [25]. In a randomized controlled trial ($N = 104$), taking aged garlic extract (2400 mg daily for 1 year) slowed the development of coronary artery calcification and progression to coronary atherosclerosis, with a significant decrease in systolic blood pressure, in cardiovascular disease patients [10]; also, aged garlic extract decreased the cardio-ankle vascular index, a measure of endothelial function and arterial stiffness, over a three-month period in subjects with type 2 diabetes mellitus ($N = 65$) [11]. In a randomized, placebo-controlled study, black garlic, given for 6 months, improved heart function, as measured by walking distance, left ventricular ejection fraction (LVEF), and quality of life, in patients with coronary artery disease [12]. The preventive effect of garlic on atherosclerosis has been attributed to its ability to reduce the lipid content in the arterial membrane. Allicin, S-allyl cysteine, present in aged garlic extract and diallyl disulfide, present in garlic oil, are the active compounds responsible for the anti-atherosclerotic effect [13].

Many in vitro and in vivo studies are done to know the cancer-preventive effects of garlic preparations and their respective components. It is apparent that garlic contains a large number of potent bioactive compounds with anticancer properties, largely derived from allyl sulfide. Different garlic derivatives have been reported to modulate an increasing number of molecular mechanisms in carcinogenesis, such as DNA adduct formation, mutagenesis, free radical scavenging, cell proliferation and differentiation, as well as angiogenesis [14]. A matched case-control study in a hospital was conducted to explore the association between dietary Allium consumption and breast cancer risk among Iranian women and it shows that high consumption of certain Allium vegetables, particularly garlic and leek, can reduce the risk of breast cancer [15]. In rodents, garlic and its components have been reported to inhibit the development of chemically induced tumors in the liver, thus showing tumor cell growth inhibition and chemopreventive effects [16, 17]. It diminishes the tumor cell growth in the prostate, bladder, and stomach [18–20].

Extracts of garlic and its related phytochemicals have anti-inflammatory potential also. One study reported that garlic extracts markedly affected liver inflammation and damage caused by *Eimeria papillata* infections [21], and a meta-analysis of ten trials and one observational study found that garlic intake of 2–2.4 g/day for four weeks or longer decreased levels of the inflammatory mediators tumor necrosis factor-alpha (TNF-α), highly sensitive C-reactive protein (CRP), and interleukin (IL)-6, supporting the use of garlic as an adjuvant treatment for metabolic diseases [22]. The anti-inflammatory activity of garlic is caused by the inhibition of the emigration of neutrophilic granulocytes in the epithelia. Aged black garlic (ABG) has shown potent antioxidant activities and these activities may be responsible for its anti-inflammatory activity [23, 24].

1.2 Aloe vera

Aloe barbadensis Miller commonly known as *Aloe vera* is the most popular natural product in the prevention and ailment of various health problems and maladies. It belongs to the family Asphodelaceae (Liliaceae). It is native to subtropical regions and tropical climates. There are more than 400 species of *Aloe* belonging to family Liliaceae. The main characteristic of the *A. vera* plant is its high water content, which ranges between 99 and 99.5% [26]. The remaining 0.5–1.0% solid material contains over 75 different potentially active compounds, including water-soluble and fat-soluble vitamins, minerals, enzymes, simple/complex polysaccharides, phenolic compounds, and organic acids [27]. Distinctive mechanisms have been proposed for the wound-healing effects of *Aloe vera*. Glucomannan, a polysaccharide rich in mannose, and gibberellin, a growth hormone, interact with growth factor receptors on fibroblasts, stimulating their activity and proliferation, which in turn significantly increases collagen synthesis after topical and oral *Aloe vera* [28]. A study revealed that *Aloe vera*-based and chitosan-based hydrogel gels exhibited wound-healing effects and high biocompatibility with seeded mesenchymal stem cells used for healing grade II burns in rats [50]. In a randomized controlled clinical trial, a polyherbal cathartic capsule of Shou Hui Tong Bian, containing *Polygonum multiflorum* and *Aloe vera*, improved arthroscopy, replacement efficacy, recovery time, time to postoperative exhaustion of borborygmus, and abdominal distention in postoperative patients ($N = 98$) after joint replacement arthroscopy compared to conventional treatment [29]. In a meta-analysis (23 studies, $N = 4023$), the authors conclude that *Aloe vera* may have beneficial effects in reducing pain scores and the severity of mucocutaneous conditions, such as psoriasis, burns, and wound healing, compared to placebo [30]. Abbasi reported that in a double-blind RCT of 28 patients, use of a topical skin ointment containing *Aloe vera*, honey, and peppermint as a dressing for skin graft donor sites was superior to petroleum jelly in reducing wound erythema and improved treatment satisfaction [31]. In a clinical study, to verify the effectiveness of *A. vera* gel compared to silver sulfadiazine 1% cream as a burn dressing for the treatment of superficial and partial burns, burn wound healing was significantly earlier in patients treated with *A. vera* than patients treated with 1% silver sulfadiazine [32]. Polysaccharides isolated from *A. vera* induce matrix metallopeptidase (MMP)-3 and metallopeptidase inhibitor-2 gene expression during rat skin wound repair, which directly helps regulate the wound-healing activity of *A. vera* gel in rats [33]. *Aloe vera* enhanced the efficacy of topical human vascular endothelial cell transplantation on excised full-thickness skin wounds in diabetic mice in improving angiogenesis in part by improving glycemic control. Oral administration also promoted wound healing through inhibition of MMP-2 and MMP-9 expression [45].

Clinical studies have suggested that *A. vera* gel may act as a safe anti-hyperglycemic and anti-hypercholesterolemic agent for patients with type 2 diabetes without any significant effects on other normal blood lipid levels or liver or kidney function [34]. A polyherbal formulation, including *Aloe vera*, was tested in

an open-label phase I trial in 30 patients who had hyperlipidemia and hyperglycemia [35]. The formulation was found to be safe and effective in lowering blood glucose and serum lipid levels in patients with type 2 diabetes [9]. In a randomized controlled trial, *A. vera* gel complex reduced body weight, body fat mass, and insulin resistance in obese prediabetics and untreated early diabetic patients [36]. Jain et al. found that *A. vera* gel has significant antidiabetic and cardioprotective activity because it significantly reduces oxidative stress in streptozocin-induced diabetic rats and improves antioxidant status [37]. *A. vera* also showed improvement in the function of isolated rat pancreatic islets in which it increased islet cell survival, their mitochondrial activity, and insulin levels while reducing the production of reactive oxygen species [38].

Aloin, a natural compound anthraquinone and the main component of *Aloe vera*, has been documented for its momentous potential therapeutic options in cancer, showing chemotherapeutic effects against 1,2-dimethylhydrazine induced by preneoplastic lesions within the colon of Wistar rats [39]. In recent studies, a polysaccharide moiety has been shown to inhibit the binding of benzopyrene to primary rat hepatocytes, thereby preventing the formation of potentially carcinogenic benzopyrene-DNA adducts. An induction of glutathione S-transferase and an inhibition of the tumor-promoting effects of phorbol myristic acetate were also reported, suggesting a possible benefit of using *Aloe* gel in cancer chemoprevention [40, 41].

A. vera leaf extricates have been advanced for digestion and are utilized within the treatment of peptic ulcer for cytoprotective activity whereby *A. vera* gel expresses antibacterial properties against both susceptible and resistant *Helicobacter pylori* strains and acts as a novel effective natural agent for combination with antibiotics for the treatment of *H. pylori* gastric infection [42]. One study illustrated that newly designed *Aloe*- and myrrh-based gels demonstrated to be effective in the topical application of minor recurrent aphthous stomatitis and was prevalent in diminishing ulcer size, erythema, and exudation; myrrh resulted in greater pain reduction in a randomized, double-blind, vehicle-controlled study [43]. Local application of *Aloe vera*/*Plantago major* gel in addition to routine care was evaluated in patients with diabetic foot ulcer. Patients in the experimental group demonstrated significantly reduced ulcer surface and total ulcer score, but not ulcer depth [44]. Acetyl polysaccharides from *Aloe vera* leaf gel showed antioxidant and anti-inflammatory effects against ulcerative colitis in rat serum and colon tissue by attenuating colon lesions and increasing short-chain fatty acids likely via upregulation of Zonula occludens-1 (ZO-1), occludin, NAD(P)H Quinone Dehydrogenase 1 (NQO1), and nuclear factor erythroid 2-related factor 2/heme oxygenase-1 (Nrf2/HO-1) signaling pathways [47].

Several studies have been conducted to test the antioxidant property of *A. vera*. Oral administration of *Aloe vera* leaf gel showed anti-inflammatory and antimicrobial effects against parasitic cryptosporidiosis in immunocompetent and immunosuppressed mice with dexamethasone by reducing the levels of interferon-gamma (IFN-γ), IL-4, IL-6, and IL-17, and a reduction in *Cryptosporidium* DNA or oocysts in stool samples compared to nitazoxanide [46]. Oral administration of a proprietary *Aloe vera* gel formula normalized pro-inflammatory and anti-inflammatory

cytokines and increased relative abundance of *Bacteroides*, *Butyricimonas*, *Ruminococcus*, and *Mucispirillum* in diabetic mice induced by a high-fat diet [48]. Applying *Aloe vera* gel to experimentally induced penile fractures in rats without closing the sutures reduced the degree of inflammation in the area [49]. Compared with control, a new wound dressing composed of alginate and *Aloe vera* gel and cross-linked with zinc ions exhibited anti-inflammatory activity, stimulated angiogenesis in the proliferative phase, increased type I collagen fibers, and decreased type III collagen fibers in rats compared to control [51]. *Aloe vera* gel improved lipid peroxidation and oxidative stress, reduced creatine phosphokinase MB (CK-MB) enzymatic activities and glutathione concentration, increased antioxidant activities, reduced inflammatory cell infiltration, and prevented left ventricular fibrosis in rats with isoprenaline-induced myocardial infarction [52].

In rats exposed to cartap and malathion, pretreatment with aqueous extract of *Aloe vera* demonstrated marked hepatoprotective effects by reducing the oxidative stress induced by pesticides [53]. Pretreatment with 30 mg/kg *Aloe vera* attenuated liver injury with ischemia and reperfusion in a small rat study as evidenced by decreased levels of malondialdehyde (MDA) in liver tissue, higher levels of SOD, catalase (CAT), and GSH-Px, and decreased pathological tissue change and immune activity score in the inducible nitric oxide synthase (iNOS) system compared to the control group [54]. Jung et al. found that in a rat model of thioacetamide-induced hepatic retinopathy, aloin suppressed liver damage and swelling of Müller cells through normalization of Kir4.1 and aquaporin-4 channels. The results indicate that aloin may be useful in protecting retinal damage associated with liver failure [55].

1.3 Smilax

Smilax ornata, genus of flowers inside the family Smilacaceae (Liliaceae), commonly called as sarsaparilla, includes approximately 300 species of woody or herbaceous vines, variously called catbriers and greenbriers. It is mainly found in temperate, tropical, and subtropical zones worldwide. The roots of that flora had been used for hundreds of years in Asia and the Americas as a tonic, diuretic, and sudorific. The rhizome, roots, stems, and leaves of sarsaparilla are utilized in traditional medicine [58]. In recent years, interest in the study of the genus *Smilax* has increased. The study of the genus Smilax has drawn more attention recently. Reviews exist about the antioxidant properties described as a 2,2-diphenyl-1-picrylhydrazyl (DPPH•) radical scavenger. The phenolic chemicals stilbenes, flavones, flavanones, flavonols, smilasides, smiglasides, and helionosides are responsible for this affiliation [66].

Smilax glabra showed protective effects against lead-induced renal oxidative stress, inflammation, and apoptosis in weaning rats and human embryonic kidney-293 (HEK-293) cells. Hence, it is a natural antioxidant and anti-inflammatory agent for the treatment of lead-induced nephrotoxicity [56]. Astilbin at 5.3 mg/kg reduced joint damage in the hind paw of complete Freund's adjuvant (CFA)-induced arthritic

rats. Astilbin exhibited remarkable inhibitory effects on TNF-α, IL-1β, and IL-6 mRNA expressions and these effects showed inhibition of cytokine production and inflammatory response in test mice close to anti-rheumatic drug, leflunomide [61]. The methanol extract of *Smilax* 400 mg/kg claimed to produce anti-inflammatory activity in the bradykinin-prompted and prostaglandin-induced edema models [65].

Kwon et al. suggested a novel molecular mechanism for water extract of *Gleditsia sinensis* thorns (WESGR)-mediated anti-prostate cancer effects at particular steps such as with migration and adhesion to collagen, and it could provide the possibility of therapeutic utilization of WESGR against prostate cancer progression [57]. She et al. observed that the supernatant of water-soluble extract from *Smilax glabra* Roxb. (SGR) should enhance adhesion, inhibit migration and invasion of HepG2, M.D. Anderson - Metastatic Breast 231 (MDA-MB-231), and T24 cells in vitro, as well as diminish metastasis of MDA-MB-231 cells in vivo. Outcomes of F-actin and vinculin dual staining showed the improved focal adhesion in SW-dealt-with cells. Microarray evaluation indicated a repression of transforming growth factor-beta (TGF-β1) signaling by means of SW remedy, which became verified by real-time reverse transcription-polymerase chain reaction (RT-PCR) of TGF-β1-associated genes and immunoblotting of transforming growth factor beta receptor I (TGFBR1) protein [60]. Song et al. observed the growth inhibitory action of *Smilax* by treatment of its water-soluble extract 3.5 μg/μL on multiple cancer cells in vitro and in vivo, and redox-dependent persistent activation of extracellular signal-regulated kinase 1 (ERK1/2) [62]. Another study revealed that SGR inhibited growth of human breast cancer mobile line Michigan Cancer Foundation-7 (MCF7), colon carcinoma mobile line human colorectal adenocarcinoma cell line (HT-29), and gastric cancer cellular line human gastric cancer cell line (BGC-823) in a dose-structured way [63].

Huang et al. obtained total flavonoids (which include four marker compounds) of *S. glabra*, and the full content became as much as 55.6%. The consequences recommended that total flavonoids of *S. glabra* (TFSG) has huge effect on reducing uric acid in hyperuricemic mice by means of inhibiting the xanthine oxidase (XOD) sports and upregulating the expression of renal organic anion transporter 1 (OAT1) and organic cation transporter novel family member 2 (OCTN2) and their mRNA in kidney tissue of hyperuricemic mice [59].

A study revealed that SGR extract inhibited the HepG2 and Hep3B cell growth by causing cell-cycle arrest at either S phase or S/G2 transition and induced apoptosis, evidenced by a DNA fragmentation assay [64]. In vitro assay demonstrated the antioxidant potential of *Smilax*. The *Smilax* triggered a big reduction of the formalin-evoked flinches in rats, an effect reversed through opioid antagonist naloxone [66]. Rafatullah et al. studied the effect of ethanol extract of sarsaparilla 100 mg/kg/day for 90 days on carbon tetrachloride (CCl4)-induced hepatocellular damage in rats [67].

Nithyamala et al. investigated analgesic interest of root powder of *Smilax* by means of hot plate technique and acetic acid prompted writhing technique in albino mice. The oral administration of root substantially expanded the response time in a dose-based manner in warm plate technique. The basis powder also induced

inhibitory impact on writhing triggered by using acetic acid [68]. Methanolic extract of *Smilax* roots examined for its immunomodulatory interest by means of nitro blue tetrazolium chloride (NBT) reduction test and anti-arthritic test by in vitro protein denaturation and in vivo complete Freund's adjuvant (CFA) precipitated arthritis. Extract at 200 mg/kg and 400 mg/kg showed statistically significant inhibition ($p < 0.05$) of the edema formation in CFA model [69].

Leaf and fruit extracts of *Smilax* were shown to exhibit antimicrobial and antioxidant activities, which may be attributed to the presence of secondary metabolites such as alkaloids, flavonoids, tannins, triterpenoids, and sterols [73]. In vitro antioxidant activities of leaf and stem extracts of *Smilax* were performed, which revealed the reducing power of leaf and stem extracts of *Smilax* [70]. Another study revealed marked reducing activity of methanolic extract of stem when compared to aqueous extract of stem [71]. Muthu et al. investigated the evaluation of in vivo antioxidant activity of ethanolic extract of root on aluminum-chloride-induced apoptosis suppressing antioxidative stress in Wistar rats and found that *Smilax* can be used as an antioxidant that is beneficial in preventing the progress of various oxidative stresses [72].

1.4 Meadow Saffron

Meadow saffron, *Colchicum autumnale*, belonging to family Liliaceae is a flowering species. It is native to mountains in wet grasslands – Turkey and Balkans [81]. It is also known as autumn crocus [74]. Meadow saffron is claimed to have many therapeutic uses such as anti-inflammatory, antitumoral, possible inhibition of viral replication, inhibitory effect on coagulation activation, and antifibrotic. It is useful in treatment of gout and Behçet's disease. The therapeutic activity of this plant is attributed to the presence of alkaloids or, in other words, colchicinoids such as colchicine and demecolcine [75–78]. Colchicine's benefits in the treatment of cirrhosis, psoriasis, and amyloidosis have been made evident by researchers [79]. Bioactive phenolic compounds such as lignans, flavonoids, phenolic acids, and tannins are also distributed in meadow saffron [80].

A randomized, multicenter, controlled, open-label parallel group (2:1 ratio), phase III clinical trial demonstrated that early administration of colchicine has clinical effectiveness in reducing the complications of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in a population highly susceptible, and may mitigate the health crisis and prevent the collapse of the health system in the successive waves of the coronavirus pandemic [83, 84].

Colchicine has been known as a treatment for gout for several millennia. Aggravation in gout is intervened by a combination of neutrophil and macrophage activation, leukocyte adhesion molecules, inflammasome actuation, and IL-1β production. It is reported that all of these pathways are influenced by colchicine [85]. Mikkelsen et al. prepared a crystalline alkaloid, desacetyl-methyl-colchicine, from bulbs of *C. autumnale* for the clinical trial in certain hematologic disorders and

acute gout in a 51-year-old patient with history of recurrent acute episodes of arthritis [82]. In a randomized placebo-controlled trial evaluating the efficacy and toxicity of colchicine in acute gout, patients were treated with an initial dose of 1 mg followed by sequential doses of 0.5 mg every two hours until either significant symptomatic relief or intolerance. Patients treated with colchicine were observed to experience pain relief within 48 hours as compared to placebo [86]. The AGREE—Acute Gout Flare Receiving Colchicine Evaluation—trial was the first randomized, placebo-controlled trial to compare low- and high-dose colchicine and it was observed that there is a comparable response rate in the low-dose group versus high-dose group [76]. Also, high-dose group showed more side effects like diarrhea and nausea [76]. A placebo-controlled randomized trial evaluating colchicine for flare prophylaxis in patients with chronic gout initiating allopurinol found that subjects treated with colchicine had fewer and less severe flares [87].

In a randomized controlled clinical trial, two groups were divided: the patients in the intervention and control groups were treated with Rhazes tablet + Ibuprofen pearl (400 mg) PRN (pro re nata) and placebo tablet + Ibuprofen pearl (400 mg) PRN, respectively. It was concluded that Rhazes tablet can be used as a pharmacological intervention to reduce pain in patients with lower back pain [83].

Since 1974, colchicine is the treatment of choice for Familial Mediterranean Fever (FMF). It is evident through a randomized controlled trial in which patients were treated with colchicine and fewer attacks were observed [88]. A randomized cohort study showed favorable efficacy of colchicine in treatment of secondary amyloidosis [89]. Colchicine was found more effective than melphalan and prednisone in increasing the survival rate of patients [89].

Colchicine was reported to be used in Behçet's syndrome; 7–12 patients were reported to show improvement in symptoms when treated with colchicine 0.5 mg twice a day [90]. A double-blind controlled trial wherein 116 sufferers with Behçet's syndrome were randomized to get hold of either colchicine or placebo for 2 years showed enormous reductions in the occurrence of genital ulcers, erythema nodosum, and arthritis in woman patients, in addition to a decrease in the incidence of arthritic signs in men [91, 92].

All parts of the plant, especially the bulbs, are highly toxic. If taken in abundance it can be highly toxic and can be fatal. Cramping, vomiting, diarrhea, increased blood pressure, and respiratory failure are the poison symptoms [93]. Formerly, poisoning occurred when people used homemade preparations. Due to this, many deaths have been reported [94].

1.5 Asparagus

Asparagus officinalis is a medicinal plant belonging to family Liliaceae. It is native to temperate Himalayas and includes about 300 species around the world. It is beneficial in treating leprosy, dysuria, epilepsy, night blindness, jaundice, disorders of the kidney and liver, as well as being anticancer, antidiabetic, anti-inflammatory, diuretic, increase fertility, lessen menstrual cramps, and laxative [95, 96]. The main

bioactive constituents of asparagus are a group of steroidal saponins. This plant also contains vitamins A, B1, B2, C, and E, as well as Mg, P, Ca, Fe, and folic acid. Other primary chemical constituents of asparagus are essential oils, asparagine, arginine, tyrosine, flavonoids (kaempferol, quercetin, and rutin), resin, and tannin [97, 98]. Saponins have a wide range of biological activities, including those of antioxidants, immunostimulants, antihepatotoxic, antibacterial, beneficial for diabetic retinopathy, anticarcinogenic, antimicrobials, that inhibit molds, antidiarrheal, and antiulcerogenic agents [97, 99].

The hypoglycemic effects of asparagus extracts were evaluated by streptozotocin (STZ)-induced diabetic rats, which had the same efficacy at a dose of 500 mg/kg as the antidiabetic drug glibenclamide (5 mg/kg rat body weight) [100]. Asparagus juice (CAJ) from asparagus old stem was used in type I diabetic rat model, and results showed that CAJ reduced the blood glucose level along with lipid level in diabetic rats by decreasing the content of serum glucose, total cholesterol, and MDA, and improved level of serum insulin [101]. Hypoglycemic activity of asparagus old stem was also reported by Zhao (2010). He reported the presence of flavonoids, polyphenols, saponins, and polysaccharides, which showed remarkable hypoglycemic effects at 1.43, 5.58, 1.82, and 4.24 mg/g dry weight, respectively [102]. The extract of *A. officinalis* in the diabetic rats showed potent antioxidant activity and improvement in β-cell function both at 250 mg/kg and 500 mg/kg. The insulin–glucose ratio was reported to increase at both doses [103].

A. officinalis also shows antitumorigenic and antimetastatic effects. In a transgenic mouse model of high-grade serous ovarian cancer, asparagus was reported to decrease the cellular viability and caused cell-cycle G1 phase arrest. It inhibited tumor growth and increased phosphorylation of adenosine monophosphate-activated protein kinase (AMPK) in the ovarian tumor tissues [104]. The inedible bottom part of asparagus was utilized as a supplement and the saponins from old stem of asparagus suppressed the cell viability of breast, colon, and pancreatic cancers. The extract inhibited the tumor cell motility [105]. The popular vegetable dish of asparagus, i.e., the shoots of white asparagus, was reported to possess antioxidant, anti-inflammatory, and antitumor activities. The Wistar rats with induced colon carcinogenesis were treated with asparagus for seven weeks and the rats exhibited a 50% reduction in the amount of pre-neoplastic lesions and promoted normal cellular homeostasis [106]. Xiang et al. also reported the anticancer effects of asparagus. Deproteinized asparagus polysaccharide exhibited widespread anticancer activity in opposition to hepatocellular carcinoma cells and sensitized the tumoricidal consequences of mitomycin, indicating that asparagus is a chemosensitizer for liver cancer therapy [107]. Mechanistic studies revealed the inhibition of migration, invasion, and angiogenesis of cancer cells [108].

Asparagus showed antioxidant, anti-inflammatory, and antihepatotoxic properties in the 40 Wistar rats that were given 400 mg/kg of the extract. Asparagus extract increased the total antioxidative capability and improved function of liver and kidney tissues. According to the researchers, it has a potential protective action against oxidative stress, and liver and kidney damage [109]. Also, asparagus seed extract additionally accelerated general antioxidant reputation at a dose of 500 mg/kg in

streptozotocin-induced diabetic rats [100]. Ku et al. (2017) reported the high binding capacity of soluble polyphenols of asparagus to human serum albumin and it also showed the protective effects against bisphenol-A-induced toxicity [110].

Asparagus has potential against bile acids, which are the important excretory pathways for cholesterol metabolism. Asparagus effect was studied on cholesterol as it reduced the simulating gastrointestinal digestion and measured binding capacity of the food and bile acid [98]. Another study indicated the cholesterol-lowering activity of asparagus in hyperlipidemia mouse model; polysaccharides present on asparagus lowered the lipoprotein cholesterol [111, 112]. Asparagus also showed the positive results in lowering the blood pressure from human clinical trials and therefore can be used as an antihypertensive agent [113].

There are various other therapeutic as well as physiological effects of asparagus. The instant powder of asparagus increased the sleep time in insomnia patients, and also shortened the sleep time through the food test that was performed on 60 volunteers [114]. Jager et al. (2005) proved the antiepileptic activity of asparagus instant powder [115] and Miura et al. (2016) discovered the stress-relieving property [116].

1.6 Lily of the Valley

Lily of the valley is a common name of *Convallaria majalis*. This plant belongs to Liliaceae family. The plant contains numerous steroidal glycosides, cardiac glycosides, flavonoids, chelidonic acid, choline, and azetidine-2-carbonic acid. In rhizomes and roots of the plant, steroidal saponins are predominant [117–120]. From ancient times, lily of the valley is used for the treatment of various cardiovascular ailments including congestive heart failure, cardiomyopathy, irregular heartbeat, urinary tract infections (UTIs), kidney stones, epilepsy, edema, and various eye infections. It is also used in the treatment of leprosy [121]. An ointment made from the roots is used in the treatment of burns and to prevent scar tissue. However, owing of the plant's potential toxicity, it should never be used without first consulting a professional [131].

Cardiac glycosides, also known as cardenolides, are a type of steroid that has long been known to have a positive ionotropic impact on the heart. All cardiac glycosides increase intracellular sodium by affecting ion transport across cardiac muscle cell membranes via effects on Na(+)/K(+)-ATPase enzymes. As a result, intracellular calcium levels rise, improving heart contractility. Atrial flutter and fibrillation are also converted to steady sinus rhythm with cardiac glycosides [123, 124].

Convallaria majalis has been demonstrated in animal trials to raise K+ in the atria and atrial stroke volume. Despite the fact that convallatoxin is a vasoconstrictor, the sum of all cardiac glycosides and other ingredients may have a greater vasotonic effect, improving circulation and coronary flow [125, 126].

A study was done for the determination of whether convallatoxin present in the plant as a cardiac glycoside induces the expression of tissue factor and leads to

hypercoagulable state. The findings indicate that the convallatoxin induces the tissue factor expression in endothelial cells and also induces hypercoagulable state [122].

Convallaria majalis is a homoeopathic medicine that has a beneficial effect on the heart and also acts as a diuretic. Lateef et al. (2010) evaluated the effect of lily of the valley on kidney function by investigating the effect of plant extract on serum uric acid and creatinine on rabbits for 14 days. After the completion, animals were sacrificed to collect blood sample. It was concluded that the alcoholic extract at 10 mg/kg acts as a significant hypouricemic agent [127].

Another study indicated the effect of convallamaroside, i.e., the steroidal saponin present in *Convallaria majalis.* Isolated extract was injected to the mice and evaluated by intradermal test. Convallamaroside medication to mice reduced the number of new vasculatures produced by sarcoma mouse cells ($p = 0.001$) [128].

For a single ingredient, convallatoxol, the dose that killed 50% of a sample population (LD50) in cats was 0.14 mg/kg given intraperitoneally [130]. This herb's human dose is 0.6 g powdered herb or 5–10 drops tincture, split daily. A case report detailed a dog that died abruptly after consuming lily of the valley in its enclosed yard [129].

The essential oil of lily of the valley is used in aromatherapy to treat headaches, depression, and melancholy. Memory loss, apoplexy, and epilepsy can all be treated with it. It is utilized to help brain cells grow stronger and to boost cognitive functions. UTI is treated with a tincture made from lily of the valley flowers, which clears blockages from the urethra. Because of its purgative and laxative properties, this herb is commonly used as a substitute for aloes. This, in turn, keeps the digestive system running smoothly.

The lily of the valley also has the following advantages:

- Kidney stones are broken down.
- Prevents the body from retaining water.
- Pain associated with joint tissues such as gout and rheumatism are reduced.
- Conjunctivitis is treated with this medication.
- Paralysis, shock, and speech loss are all treated using essential oils.
- Aids in the treatment of leprosy and edema.
- Poisoning and drunkenness are treated by producing vomiting.

2 Conclusions

Natural products act as very potential products for new drug discovery and have the ability to generate new drug leads that will be further subjected for clinical trials. In the present study, several advances in the field of technology of natural products were discussed and how they are subjected for clinical trials were described in detail. In this chapter, several conclusive points were also discussed on the basis of analyzed data and therapeutic-evidence-based studies, which provide a very strong

basis for the conduction of natural-products-based-drug clinical trials to continue for making major contributions toward change in human health and maintenance of longevity without any serious adverse effects. There is also a requirement for further studies to provide more powerful evidence of the adverse effects concerned with the drugs discussed above. In addition, the safety of consumption of aforementioned compounds in definite conditions and diseases should also be noted down. Furthermore, after considering all the evidence-based facts and conditions, it seems that natural products can be utilized to provide various health-promoting properties.

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