Chapter 12
Role of Dietary Supplementation of Natural Products in the Prevention and Treatment of Liver Diseases

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Abstract The practice of medicine using either natural agents as they are or derivatives of natural products for treating the human diseases is commonly referred to as "natural medicine" or "naturotherapy." The usage of naturotherapy has been there for thousands of years for many human diseases. Naturopathy medication, by definition, must exist in the nature, and is generally used without addition of any chemicals, without or with marginal processing. Herbs, diet supplements, plant derivatives, nutrient supplementation, etc. generally fall into the category of natural medication. Liver, being the most important in detoxification of chemicals and major regulator of body energy storage and expenditure as well as the central hub of metabolic activity, is constantly under the pressure of getting damaged. Humans encounter many liver diseases like alcoholic liver disease, nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, cirrhosis, hepatitis, and cancer. The prevalence of liver diseases is increasing each year, demanding the high need for developing effective therapies. Although, over the years, we have achieved a considerable advance in liver disease prevention, screening, diagnostic, and treatment methodologies, the rate of liver diseases is in continuous rise. In addition, because targeted therapy for liver diseases is not much successful till now, the appreciation related to traditional herbal medicine is constantly increasing. In this chapter, we discuss briefly few of the herbal plants, which showed efficacy in in vitro studies. We also highlight the preclinical evaluation undertaken for each of these plants towards the goal for healing a variety of liver diseases.

Keywords Naturopathy · Natural medicine · Herbal medicine · Herbal plants · Liver disease · Hepatocellular carcinoma · Liver cirrhosis

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Abbreviations

ACP	Acid phosphatase
ALD	Alcoholic liver disease
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST/SGOT	Serum glutamic-oxaloacetic transaminase
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
LC	Liver cirrhosis
LP	Liquid paraffin
LPS	Lipopolysaccharide
NAFLD	Nonalcoholic fatty liver disease
NASH	Nonalcoholic steatohepatitis
PPARα	Peroxisome proliferator-activated receptor-alpha
SREBP-1	Sterol-regulatory element-binding protein-1

1 Introduction

Liver is the largest gland of the body weighing about 1.4 kg in average adult. The most impressive fact about liver is its potency to regenerate completely even with a minimum of $1/4^{th}$ of the tissue remaining, without interruption of its functions. It has both secretary and excretory functions such as (1) metabolism of carbohydrates, proteins, and lipids; (2) storage of vitamins and minerals; (3) processing of drugs and hormones; (4) synthesis of bile salts; (6) supporting blood clot formation; (7) phagocytosis; (8) hematopoietic function; (9) hemolysis; (10) activation of vitamin D; and (11) excretion of bilirubin. It is not of much surprise that liver is more prone to diseases, as it performs many multidimensional functions. Intake of high-fat diet, high alcohol consumption, and exposure to harmful pollutants/carcinogens often lead to various chronic liver diseases like hepatitis (HBV or HCV related), ALD, NAFLD, NASH, LC, and HCC in humans. With each passing year, there has been increasing evidence supporting a very high prevalence of these liver diseases; among that HCC is the sixth most commonly diagnosed cancer and fourth leading cause of cancer deaths worldwide and it alone contributes to 782,000 deaths in 2018. According to the GLOBOCAN reports 841,000 new cases were reported with HCC in 2018 [1]. In a meta-analysis, the global prevalence of NAFLD is 25.2% and NASH is between 1.5% and 6.5% [2]. A modeling study conducted in the United States estimated that the prevalence of NASH will increase up to 63% by 2030, which ultimately leads to increased incidence of NASH-related diseases like cirrhosis, HCC, and deaths [3]. Although there are great advances in the prevention, screening, and novel technologies in the diagnosis and treatment, the survival rate

remains low. The efficiency of current synthetic therapeutic agents like cisplatin, 5-fluorouracil, doxorubicin, orlistat, sibutramine, and rimonabant in treating chronic liver disease is not satisfactory and these chemicals have undesirable side effects. Moreover, some diseases like NAFLD and NASH have no FDA-approved therapy till date [4]. Thus, in order to prevent and treat these liver diseases, effective medications and treatment strategies need to be developed. In that scenario, plants and plant derivatives seem like torchbearer to the modern research. There is a constant increase in the research investment in traditional herbal medicine, which was previously underappreciated. In this chapter, we briefly discuss various herbal plants, which showed efficacy in in vitro studies, as well as highlight their preclinical evaluation for treating various liver diseases (Table 12.1).

1.1 Andrographis paniculata *(Burm. f.) Nees (*A. paniculata*)*

Andrographis paniculata (Acanthaceae), commonly known as the "king of bitters," is a renowned hepatoprotective and hepatostimulant agent [5]. Along with its hepatoprotective activity, this plant is also traditionally used for curing diabetes [6], malaria [7], and snake bite. Protective effects of this plant are credited to the presence of major phytoconstituents "andrographolide and arabinogalactan" [8].

Preclinical Studies Preclinical studies by Singha et al. proved that intraperitoneal administration of andrographolide and arabinogalactan protein of *A. paniculata* is responsible for hepatoprotective effects. Reduction in the levels of biochemical parameters (AST, ALT, ACP, ALP, and LP) in the liver and kidneys is indicative of its benefit [8]. There are studies reporting that *A. paniculata* exhibits hepatoprotective effects against thioacetamide (TAA)-induced hepatic fibrogenesis and cirrhosis in rats by decreasing collagen production and inflammation response in the mice [9, 10]. It was reported that, in adult male rats, ethanol extracts of *A. paniculata* inhibit intrahepatic cholestasis by regulating the NF-κB signaling [11]. The treatment with andrographolide protects the liver from H_2O_2 and LPS/D-GalN-induced liver damage [12, 13].

1.2 Amaranthus spinosus *Linn*

Amaranthus spinosus L. (Amaranthaceae) commonly known as "chaulai" is an annual herb distributed all over the world. The leaves of *A. spinosus* have high medicinal value. It is used to ward off swelling around stomach and to cure hepatic disorders, jaundice, scanty urine, and wounds [14, 15]. *A. spinosus* is well known for its antimalarial [16] and antioxidant properties [17]. *A. spinosus* comprises a number

of bioactive components like kaempferol, diglycosides, quercetin, amaranthine, isoamaranthine, betanin, isobetanin, and hydroxycinnamates [18].

Preclinical Studies In an in vivo study by Hussain et al., alcoholic extract of *A. spinosus* showed potential hepatoprotective activity [19]. Results of yet another finding revealed that 50% of ethanolic whole-plant extract of *A. spinosus* protects the liver against D-galactosamine/LPS-induced liver injury in rats [20]. All these results signify the potential application of this herb for treatment against liver problems.

1.3 Cynara cardunculus

Cynara cardunculus L. (Asteraceae), generally known as artichoke, is a perennial thistle. This plant is vastly distributed in Southern Europe, where it is consumed as vegetable and is also formulated in herbal tea. The extracts of *C. cardunculus* have been widely used since decades in folk medicine to treat hepatitis, diabetes, rheumatism, urinary stones, and various hepatobiliary diseases. It also has hypolipidemic and hypoglycemic effects [21]. Artichokes are classified as functional food [22], and the edible flower of artichoke is known to have a health protective potential and also strengthens the liver and gallbladder functions [23]. The major components of artichoke are naringenin, apigenin glycosides, luteolin-7-glucoside, and high levels of inulin [21, 22].

Preclinical and Clinical Studies Both in vitro and in vivo studies have reported the hepatoprotective, anticarcinogenic, and hypocholesterolemic functions of *Cynara cardunculus* [24, 25].

1.4 Cichorium intybus

Cichorium intybus (Asteraceae), commonly known as chicory, is a perennial herbaceous plant. In Ayurvedic medicine, chicory seeds are used in hepatobiliary disorders and in Persian folk medicine and the seeds and leaves of *C. intybus* are considered as hepatoprotective and antidiabetic [26]. The phytochemical esculetin is a phenolic compound of *C. intybus* [27].

Preclinical Studies In an in vivo study, it was reported that the extracts of *C. intybus* seeds, root, and root callus showed hepatoprotective activity against acetaminophen and CCl_4-induced hepatic damage [28, 29]. Pretreatment of rats with esculetin also prevented CCl_4 and paracetamol-induced hepatic injury [27]. Cichotyboside is a component isolated from the seeds of *C. intybus*, and exhibited hepatoprotective activity similar to silymarin against CCl_4-induced toxicity in Wistar rats [30]. Ziamajidi et al. showed that chicory seed extracts will have

ameliorative affect against oleic acid-induced non-alcoholic fatty liver disease NAFLD/NASH via modulation of PPARα and SREBP-1 [31].

1.5 Curcuma longa *L.*

Curcuma longa L. (Zingiberaceae) is commonly known as turmeric, wherein curcumin is the main active ingredient. It has been used since ages in the Indian subcontinent to treat various illnesses such as rheumatism, body pains, skin diseases, intestinal worms, diarrhea, intermittent fevers, hepatic disorders, biliousness, urinary discharges, dyspepsia, inflammations, constipation, leukoderma, amenorrhea, and colic. This research is much focused on curcumin, because of its potentiality to treat many diseases without any side effects. Curcumin has the ability to treat a wide variety of inflammatory diseases, cancer, diabetes, cardiovascular diseases, arthritis, Alzheimer's disease, psoriasis, etc., through modulation of numerous molecular targets [32]. This provides a rational molecular basis to use Curcumin for treating hepatic disorders [33].

Preclinical Studies It was reported that curcumin protects from liver injury induced by ethanol, thioacetamide, iron overdose, cholestasis, and acute subchronic and chronic CCl_4 intoxication. Furthermore, it can reverse CCl_4-induced cirrhosis to some extent [33]. *Curcuma longa* extracts also reduced the visceral fat and delayed pathogenesis in HBV-X protein transgenic mice [34]. The administration of curcumin had also reduced the hyperplastic nodules, liver damage markers, body weight, and hypoproteinemia in the liver of diethyl-nitrosamine/phenobarbital-challenged Wistar rats. It also demonstrated anticancer activity against chemical-induced hepatocarcinogenesis [35].

1.6 Cassia occidentalis

Cassia occidentalis (Fabaceae) is also known as Senna coffee/Negro coffee and it is a communal wild plant. This plant is considered as an important ingredient of several polyherbal preparations marketed for liver diseases. This plant has several biological activities such as blood purification, anti-allergic, anti-inflammatory, antioxidant [36], antinociceptive, antifungal, antidiabetic, hepatoprotective, hypolipidemic, and anti-atherosclerogenic activities [37]. *C. occidentalis* is also traditionally used to cure hepato-myo-encephalopathy and skin diseases like psoriasis and leprosy [38]. Bioactive constituents are mainly achrosin, aloeemodin, cassia occidentanol I, cassia occidentanol II, emodin, anthraquinones, anthrones, apigenin, aurantiobtusin, campesterol, cassiollin, chryso-obtusin, chrysophanic acid, chrysarobin, chrysophanol, and chrysoeriol.

Preclinical Studies Jafri et al. demonstrated the hepatoprotective role of aqueous ethanolic extract of leaves of *C. occidentalis* against paracetamol-induced liver injury. The conclusive remark was in the favor of significant hepatoprotection [39].

1.7 Citrus paradise

The common name of *Citrus paradise* (Rutaceae) is grapefruit. Grapefruit is prized for its high content of vitamin C, folic acid, phenolic acid, potassium, calcium, iron, limonoids, terpenes, monoterpenes, and D-glucaric acid. It is an incredible source of many phytochemicals and nutrients that contribute to a healthy diet. Naringin is the flavonoid in greatest concentration in the grapefruit, and in humans it is metabolized into naringenin [40, 41]. β-Carotene and lycopene are present in red and pink grapefruit varieties. It has been used in traditional medicine for its antimicrobial, antifungal, anti-inflammatory, antioxidant, antiviral, anticarcinogenic, and anti-allergic properties [42, 43].

Preclinical Studies The study conducted by Lee et al. revealed so many interesting facts about naringenin and its future perspectives. Oral administration of naringenin notably diminished DMN-induced hepatic damage in rats. It also restored natural protein levels. Finally they concluded that naringenin had anti-fibrinogenic and hepatoprotective effects, suggesting that it could be useful in the treatment of hepatic fibrosis [44]. It was reported that the administration of naringenin to rats with ethanol-induced liver injury considerably decreased the levels of ALT, AST, and thiobarbituric acid-reactive substances and significantly increased the levels of antioxidant enzymes. Further, in their study these biochemical parameters correlated well with the histological changes [45]. In a similar study, it was proved that naringenin ameliorated the cadmium-induced oxidative damage in the rat liver [46]. Taken together these findings suggest that naringenin has a therapeutic potential to treat liver diseases.

1.8 Crocus sativus *L.*

Crocus sativus L. belongs to Iridaceae family and it is native to Asia. The dried stigmas of *C. sativus* are known as saffron, and have been used as flavoring agent since ancient times. It has been used to treat various diseases like insomnia, cognitive defects, cardiovascular diseases, and cancer. The therapeutic efficiency of saffron is mainly due to its major bioactive derivatives crocin, crocetin, picrocrocin, and safranal [47, 48]. The research over the past few years revealed that saffron plays a dominant role in the pathophysiology of some important pathological conditions like atherosclerosis, metabolic syndrome, liver cancer, neurodegenerative diseases, asthma, and allergy.

Preclinical Studies Recently, the results of an in vivo comparative study of anticancer activity between saffron extracts and its bioactive component crocetin demonstrated that crocetin was more potent in inducing cytotoxicity in cancer cells than saffron extracts. The overall highlight of this research is that crocetin is a potential anticancer agent that can be used for cancer prevention and treatment [49]. In an in vivo study, crocin showed hepatoprotective activity against the oxidative stress and inflammation caused by methotrexate [50]. It was reported that the pretreatment with *Crocus sativus* petals guards the liver from the damage caused by acetaminophen in animal models [51]. Crocin administration also showed hepatoprotective activity against the liver damage induced by morphine [52].

1.9 Daucus carota

Daucus carota (Apiaceae) is the scientific name of carrot. Carrot is called as vitaminized food due to the presence of numerous phytonutrients like phenolics, polyacetylenes, carotenoids, and ascorbic acid [53]. They are considered as a functional food with significant health-promoting properties. *D. carota* is the excellent source of vitamin A to treat night blindness. Besides its antioxidant property, it also has anticancer [54, 55], antimutagenic, chemopreventive, photoprotective, and immune-enhancing properties and is also able to activate the platelets [56].

Preclinical Studies The methanolic extracts of *Daucus carota* seeds had showed hepatoprotective and antioxidant activity against thioacetamide-induced oxidative stress in experimental rat models (Singh, [57]). Bishayee et al. demonstrated that carrot extract offers a significant hepatoprotective activity against CCl_4-induced liver damage in experimental animals [58].

1.10 Eclipta alba

Eclipta alba (Asteraceae) commonly known as bhringaraj is a perennial shrub mostly found in moist tropical countries. *E. alba* contains alkaloids, flavonoids, glycosides, polyacetylenes, and triterpenoids. Wedelolactone and demethyl wedelolactone are coumestan and are also mainly found in *Eclipta alba*. In traditional medicine, it is extensively used for treatments such as to grow hair, for gastrointestinal disorders, and also as hepatoprotective and neuroprotective agent [59, 60].

Preclinical Studies The coumestan constituents of *E. alba* showed potent antihepatotoxic activities in CCL_4-, galactosamine-, and phalloidin-induced liver damage in animal models [61]. In a recent study by Naik et al., *E. alba* showed protective activities against hyperlipidemia induced by high-fat diet in animal models [62].

1.11 Ficus carica

Ficus carica (Moraceae), commonly known as fig, is a small tree grown in many countries. It has many nutritive and medicinal properties and it was widely used in ancient systems of medicine as an antibacterial, antifungal, antioxidant, and antiviral agent. Every part of this plant has a unique medicinal value. Fig fruit and roots are used to cure indigestion, anorexia, cardiovascular problems, and cancers. In addition, fig leaf is also used against the anemia [63]. *F. carica* leaves are reported to have high phenolic substance, organic acid content, and antioxidant potential than fig pulp and crusts [64]. *F. carica* is useful in treating liver and spleen disorders, and gout and leaves are especially used for treating jaundice. Furanocoumarins, psoralen, and daidzein are the phytoconstituents of *F. carica* leaves [65].

Preclinical Studies Gond and Khadabadi had reported that the petroleum ether extracts of fig leaves provided promising results in the treatment of rifampicin-induced hepatic damage in rat models [66]. Recently, in an in vivo study, *F. carica* has been shown to play a modulatory protective role in the liver and kidney against γ-irradiation. These authors have recommended that *F. carica* should be included in everyday diet [67].

1.12 Fumaria indica

Fumaria indica (Fumariaceae) is commonly called as parpata. It is a small annual herb that widely grows in plain sand lower hills. It has been used as a liver-protective agent. However the limited evidence suggests that more research should be carried out. The active components of *Fumaria indica* are protopine and fumariline [68]. *F. indica* is used as a blood purifier in skin diseases, styptic and febrifuge, and is also used in the disorder of liver in folk medicine. However, overdose of *F. indica* may cause diarrhea [69].

Preclinical Studies Rathi et al. in their study showed that butanol extracts of *F. indica* lead to hepatoprotection [70]. The effect of methanolic extract of *Fumaria indica* was evaluated in albino rats and the results demonstrated the anti-hepatotoxic activity of monomethyl fumarate [71].

1.13 Ginkgo biloba *L.*

Ginkgo biloba L. (Ginkgoaceae) is also known as maidenhair tree. The leaves of *G. biloba* occupied a unique status in Chinese traditional medicine. Ginkgo is widely used to cure Alzheimer's and dementia, and this plant has cardioprotective, anti-asthmatic, antioxidant, antidiabetic, hepatoprotective, photoprotective, and

anti-inflammatory activities [72–74]. Flavonol glycosides (quercetin, kaempferol, and isorhamnetin), shikimic acid, bilobanone, and ginkgolides are the phytoconstituents of *G. biloba*. Ginseng is a widely used drug derived from *Ginkgo biloba*. There are numerous studies showing the hepatoprotective activity of *G. biloba* [75]. However, in certain cases, it has been shown to cause skin allergic reactions [76].

Preclinical Studies Naik and Panda had reported that the oral administration of *Ginkgo biloba* phytosomes (GBP) showed remarkable hepatoprotection proportionate to silymarin [73]. In another finding, GBP exhibited hepatoprotective effects against CCl_4-induced oxidative damage [77].

1.14 Glycyrrhiza glabra

Glycyrrhiza glabra (Fabaceae) is commonly known as licorice. Glycyrrhiza species are the most important herbaceous plants in traditional Chinese medicine. *G. glabra* has diverse pharmacological activities [78]. Hippocrates prescribed *G. glabra* for the treatment of chest diseases, including dry cough and asthma. Glycyrrhizin is the major bioactive constituent and is mainly found in the *G. glabra* root. Glycyrrhizin is anti-inflammatory and antiviral by nature. It has been used for the treatment of chronic hepatitis and tumors and for the protection of liver functions. Glycyrrhizin had a protective effect against immunosuppression and an effect of reducing the incidence of sodium and water retention [79]. There are no obvious side effects reported.

Preclinical studies Intraperitoneal administration of glycyrrhizin and epidermal growth factor (EGF) has been shown to stimulate both liver regeneration and recovery of liver functions in rats after the surgical removal of 70% of the total liver [80]. Glycyrrhizin also protects the liver from LPS [81] and CCl_4-induced liver damage [82]. In an in vivo study, glycyrrhizin has been found to suppress the release of HCV particle, when it is used alone or combined with interferon [83]. In a similar study, glycyrrhizin inhibited the liver inflammation in concanavalin-A (Con A)-induced hepatitis mice model, which closely imitated the pathology of human autoimmune hepatitis [84]. In a clinical study, it was reported that lamivudine combined with glycyrrhizin is effective in controlling HBV replication in cancer patients [85]. Overall, it is noteworthy that glycyrrhizin has the therapeutic potential to prevent liver injury and hepatitis.

1.15 Phyllanthus emblica

Phyllanthus emblica (Phyllanthaceae) is commonly called as amla (Indian gooseberry). Amla is an Indian indigenous system of medicine and has eminent position in

traditional medicine all over the world. Every part of this plant has significant medicinal value. The fruits have been widely used to treat liver disorders, diabetes, cancer, diarrhea, jaundice, inflammation, blood pressure, sore throat, dry mouth, indigestion, abdominal pain, and cough [86]. Tannins, flavonoids, vitamins, amino acids, and carbohydrates are the most important constituents of *P. emblica*. Among those, hydrolyzable tannins (e.g., gallic acid, ellagic acid, corilagin, chebulagic acid, and geraniin) are predominant active constituents of *P. emblica* [87].

Preclinical Studies In a recent study, it was reported that the water extract of *P. emblica* fruits shows a protective effect on high-fat diet-induced NAFLD in SD rats [88]. Further, it significantly decreased fat accumulation and ROS production in HepG2 cells and also inhibited hepatic fibrosis in HSC-T6 cells [88]. There are a number of studies reporting that gallic acid protects the liver from injuries induced by various hepatotoxic agents, including paracetamol, sodium fluoride, cyclophosphamide, and carbon tetrachloride in vivo [89–92]. Hsu and Yen proved that intake of gallic acid reduces dyslipidemia and hepatosteatosis in high-fat diet-induced rats [93]. In a similar study, Chao et al. found that gallic acid ameliorates the NAFLD pathogenesis [94]. Like gallic acid, ellagic acid also showed hepatoprotective activity against paracetamol-, CCl_4-, alcohol-, D-galactosamine-, and concanavalin-induced hepatocarcinogenesis as well as showed antiviral properties against HBV and HCV, in murine models [95]. Corilagin was also identified to be highly effective in retarding the growth of xenografted Hep3B hepatocellular carcinoma cells [96].

1.16 Picrorhiza kurroa

Picrorhiza kurroa (Plantaginaceae) is one of the oldest medicinal plants commonly known as kutki. The root extracts of *P. kurroa* possess strong hepatoprotective activity [97]. *P. kurroa* includes chemical components such as picroside I, picroside II, and iridoid glycosides D-mannitol, cucurbitacins, kutkiol, kutki sterol, and apocynin, which are powerful anti-inflammatory agents and platelet aggregation reducers. The mixture of kutkoside and picroside I is known as picroliv. Picroliv is a highly active component of root extracts and it is primarily involved in the regeneration of liver parenchyma cells, protein, and nucleic acid synthesis and stimulates immune response during acute and chronic toxicity [98]. Since decades *P. kurroa* has been used in the treatment of anemia, asthma, obesity, malaria, stomach ache, fever, immune disorders, skin diseases, bronchial asthma, as well as viral hepatitis. It is a powerful anti-inflammatory, a cathartic, and a cholagogue agent. Picroliv and vimlin are the commercially available herbal products of *P. kurroa*. No harmful side effects have been reported yet.

Preclinical Studies Picroliv exhibits a strong hepatoprotective activity against aflatoxin B1 (AFB1)-induced hepatotoxicity [99]. In an in vivo study picroliv ameliorated the effect of cadmium-induced hepatotoxicity [100].

1.17 Scutellaria baicalensis Georgi

Scutellaria baicalensis Georgi (Lamiaceae) is often referred to as golden herb/skull cap and Huang-Qin (Chinese) and it is native to East Asian countries with over 2000 years of history. The wide array of pharmacological activities of *Scutellaria baicalensis Georgi* made the plant to be named in two ancient books, namely (1) The Classic of Herbal Medicine (written between 200 and 250 AD) and (2) Compendium of Materia Medica (published in the year 1593). *Scutellaria baicalensis Georgi* is used in the treatment of cold, lung and liver problems [101], diarrhea, dysentery, hypertension, hemorrhaging, insomnia, and respiratory infections. It shows antiviral, anticarcinogenic, free radical scavenging, antioxidant, immunostimulatory, and antiproliferative effects on vascular smooth muscle cells and hepatic stellate cells [102, 103]. Baicalein, wogonin, and wogonoside are the known flavonoids of *S. baicalensis*. Baicalein is widely explored for its medicinal properties and it is the important component of Xiao Chai Hu Tang (Chinese) or Sho-saiko-to (SST, Japanese) herbal formulations prescribed for human liver diseases [104, 105].

Preclinical Studies In an in vitro study, baicalin was proved to be able to protect hepatocytes from oxidative stress [106]. A growing number of studies had confirmed that baicalin offers hepatoprotective activity against liver injury [107–110].

1.18 Silybum marianum

The common name of *Silybum marianum* (Asteraceae) is milk thistle. The fruit of *S. marianum* contains silymarin, which is responsible for its hepatoprotective activity. Silymarin is a complex mixture of silychristin, silybin, and silymarin [111]. Silymarin is well recognized for its four main functions: (1) free radical scavenging activity, (2) membrane permeability regulation, (3) stimulation of DNA polymerase I, and (4) regeneration of liver cells and protein synthesis [112]. The extracts of this plant are used as liver tonics in traditional medicine to prevent hepatotoxicity and to solubilize the gallstones. This plant is also used for treating alcoholic liver disease, acute and chronic viral hepatitis, diabetes, hay fever, inflammation, and constipation. Legalon is a commercially available product of *S. marianum* being used in liver ailments. Mild laxative effects are reported in patients with silymarin sensitivity (Table 12.1).

Preclinical Studies Salam et al. reported that the administration of silymarin in combination with MSP showed protective activity against the CCl_4-induced hepatocellular necrosis [113]. A similar study conducted by Kim et al. provided evidence that the mixture of aloe vera and *Silybum marianum*, and *Ginkgo biloba* and *Silybum marianum*, had hepatoprotective effects against chronic and acute lesions induced by the organochlorine (OC) compound and N-nitrosodiethyl-amine (NDEA), respectively [114]. Silymarin reduces the liver injury caused by acetaminophen, CCl_4,

Table 12.1 List of herbal plants showing promise towards treatment of various liver diseases

S. no.	Name of the plant	Part used	Chemical constituent/ active component	Animal model	Hepatotoxic agent
1	*Amaranthus spinosus* (Amaranthaceae)	Whole plant	Amaranthine, isoamaranthine kaempferol, diglycosides, quercetin, betanin, isobetanin, hydroxycinnamates	Rats	LPS/D-GalN
2	*Andrographis paniculata* (Acanthaceae)	Whole plant	Andrographolide and arabinogalactan	Rats	Thioacetamide (TAA), hydrogen peroxide, and LPS/D-GalN
3	*Cynara cardunculus* (Asteraceae)				
4	*Cichorium intybus* (Asteraceae)	Seeds and root	Esculetin, cichotyboside	Rats	Acetaminophen and CCl4. Oleic acid-induced NAFLD
5	*Curcuma longa* (Zingiberaceae)	Root	Curcumin	Rats and mice	Thioacetamide, iron, and CCl4
6	*Cassia occidentalis* (Fabaceae)	Leaves	Achrosin, aloeemodin, cassia occidentanol I, cassia occidentanol II, emodin, anthraquinones, anthrones, apigenin, aurantiobtusin, campesterol, cassiollin, chrysoobtusin, chrysophanic acid, chrysarobin, chrysophanol, chrysoeriol	Rats	Acetaminophen
7	*Citrus paradise* (Rutaceae)	Fruit peel	Naringin	Rats	DMN and cadmium
8	*Crocus sativus* (Iridaceae)	Dried stigmas of flower	Crocin, crocetin, picrocrocin, and safranal	Rats	Methotrexate, acetaminophen, and morphine
9	*Daucus carota* (Apiaceae)	Seeds and roots	Phenolics, polyacetylenes, carotenoids, and ascorbic acid	Rats	Thioacetamide and CCl4
10	*Eclipta alba* (Asteraceae)	Whole plant	Coumestan (wedelolactone and demethyl wedelolactone)	Rats	Carbon tetrachloride, galactosamine, and phalloidin

(continued)

Table 12.1 (continued)

S. no.	Name of the plant	Part used	Chemical constituent/ active component	Animal model	Hepatotoxic agent
11	*Ficus carica* (Moraceae)	Roots, leaves, and fruit	Furanocoumarins, psoralen, and daidzein	Rats	Rifampicin and gamma radiation
12	*Fumaria indica* (Fumariaceae)	Whole plant	Protopine and fumariline	Rats	Carbon tetrachloride, paracetamol, and rifampicin
13	*Ginkgo biloba* L (Ginkgoaceae)	Seeds and leaves	Shikimic acid, bilobanone, and ginkgolides	Rats	CCl4
14	*Glycyrrhiza glabra* (Fabaceae)	Roots	Glycyrrhizin	Rats and mice	LPS, CCl4, and concanavalin-A
15	*Phyllanthus emblica* (Phyllanthaceae)	Fruit	Gallic acid, ellagic acid, corilagin, chebulagic acid, and geraniin	Rats	Paracetamol, sodium fluoride, cyclophosphamide, carbon tetrachloride, and concanavalin
16	*Picrorhiza kurroa* (Plantaginaceae)	Root	Picroside I, picroside II, and iridoid glycoside d-mannitol, cucurbitacins, kutkiol, kutki sterol, and apocynin	Rats	Aflatoxin B1 and cadmium
17	*Scutellaria baicalensis Georgi* (Lamiaceae)	Aerial parts	Baicalein, wogonin, and wogonoside	Rats	Iron, CCl4, and LPS/D-GalN
18	*Silybum marianum* (Asteraceae)	Whole plant	Silymarin (silychristin, silybin, and silymarin)	Rats	CCl4, organochlorine N-nitrosodiethylamine (NDEA) acetaminophen, iron, and phenylhydrazine
19	*Salvia miltiorrhiza Bunge* (Lamiaceae)	Root	Tanshinones	Rats	Iron, CCl4, and LPS/D-GalN
20	*Vitis vinifera* (Vitaceae)	Fruit and seed	Catechins, epicatechins, anthocyanidins, proanthocyanidins, and resveratrol	Rats	Methotrexate, DMN, and CCl4
21	*Zanthoxylum armatum* (Rutaceae)	Bark	Alpha- and beta-amyrins, fargesin, dictamine, berberine, xanthoplanine, armatamid, asarinin, and lupeol	Rats	CCl4

(continued)

Table 12.1 (continued)

S. no.	Name of the plant	Part used	Chemical constituent/ active component	Animal model	Hepatotoxic agent
22	*Zingiber officinale* (Zingiberaceae)	Rhizome	Gingerol, paradols, zingerone, zingiberol, and shogaol	Rats	DMN and piroxicam

The table shows the list of various herbs (along with the family they belong to) and the part of the plant and the active chemical ingredient. Various agents used in animal models for inducing hepatotoxicity and the protection given by each of the herb are also highlighted

radiation, iron overload, phenylhydrazine, alcohol, cold ischemia, and *Amanita phalloides* in animals (Chen, [115]). Silybin also exhibits significant anti-inflammatory effect in cirrhotic rat liver [116].

1.19 Salvia miltiorrhiza Bunge

Salvia miltiorrhiza Bunge (Lamiaceae) is also known as red sage/Chinese sage/ Danshen. More than 70 active components have been isolated and structurally identified from *S. miltiorrhiza* [117], and are broadly categorized into two groups: (1) hydrophilic compounds such as salvianolic acids and (2) lipophilic chemicals, including diterpenoid and tanshinones. Tanshinones are unique components to *S. miltiorrhiza*, and are not yet found in other Chinese herbs. Among the tanshinones, tanshinone I, tanshinone IIA, and cryptotanshinone are the foremost bioactive constituents with various pharmacological effects including antibacterial, antioxidant, antitumor, antiplatelet, and hepatoprotection [118] activities. *S. miltiorrhiza* can increase blood flow into the liver to reduce the potential damage by clearing the harmful substance in the liver. The extracts of *S. miltiorrhiza* (tanshinones) are traditionally used in the treatment of cardiovascular and cerebrovascular diseases, cirrhosis [119, 120], and cancer [121, 122]. Its product, Fu fang Dan shen Di wan, is the first Chinese herbal medicine approved by the FDA for clinical tests in the United States.

Preclinical Studies It was reported that the active ingredients of *S. miltiorrhiza* showed hepatoprotective effect against CCl_4-induced liver injury in rats [123]. In an interesting study, treatment of chronic iron-overloaded mice with *S. miltiorrhiza* improved the hepatic morphology, and decreased the iron deposition [124]. Oral administration of cryptotanshinone from *S. miltiorrhiza* showed hepatoprotective effects against D-galactosamine (GalN)/lipopolysaccharide (LPS)-induced fulminant hepatic failure [125].

1.20 Vitis vinifera

Vitis vinifera is commonly called as grape vine. This plant is well known for its antioxidant, anticarcinogenic, immunomodulatory, anti-diabetes, anti-atherogenic, neuroprotective, anti-obesity, antiaging, and anti-infection properties. In addition, it has chemopreventive activity against cardiovascular disease and some cancers. Grape juice and grape seeds are rich sources of flavonoids such as catechins, epicatechins, anthocyanidins, proanthocyanidins, and resveratrol [126]. Resveratrol is a polyphenolic phytochemical and there are numerous studies signifying the hepatoprotective properties of resveratrol. Resveratrol can prevent hepatic damage caused by free radicals and inflammatory cytokines [127].

Preclinical Studies It was reported that the treatment with procyanidin in a liver cancer xenograft model exerted antiangiogenic activity in a dose-dependent manner [128]. The grape seed extracts from winery waste showed anticarcinogenic activity against HCC by promoting apoptosis in cancer cells [129]. Resveratrol showed hepatoprotective activity against methotrexate-induced hepatic injury [130], DMN-induced injury [131], and CCl_4-challenged liver tissue [132]. Resveratrol had been shown to activate the pro-apoptotic pathway in vivo [133]. These studies suggest that resveratrol can be used for treating liver injury, fibrosis, cirrhosis, and hepatocarcinogenesis.

1.21 Zanthoxylum armatum

Zanthoxylum armatum DC. (Rutaceae) is commonly called as Timur (or) Nepal pepper. *Z. armatum* is a sub-deciduous shrub and is being extensively used in the Indian System of Medicine over many years [134]. The phytochemical constituent's α- and β-amyrins, fargesin, dictamine, berberine, xanthoplanine, armatamid, asarinin, and lupeol have high pharmaceutical importance [135]. *Z. armatum* has anthelmintic, stomachic, and carminative properties [134]. The fruits and seed extracts are employed as an aromatic tonic in fever and dyspepsia, and for expelling roundworms [135]. No adverse effects have been reported yet for this natural product.

Preclinical Studies It was reported that the administration of ethanolic bark extracts of *Z. armatum* for 7 days shows hepatoprotective activity against CCl_4-induced liver injury in Wistar rats. *Z. armatum* extracts enhanced the level of antioxidants; reduced the level of AST, ALT, ALP, and serum enzymes; and led to the recovery of damaged cells [136].

1.22 Zingiber officinale

Zingiber officinale (Zingiberaceae), widely known as ginger, is a perennial plant and the rhizome is extensively used as a spice all over the world. It is very potent in treating arthritis, sore throat, indigestion, dementia, muscular aches, and fever [137–139]. Ginger is characterized as functional food to its nutritional and phytochemical composition. Gingerol, paradols, zingerone, zingiberol, and shogaol are the main phytochemicals of *Zingiber officinale* [140].

Preclinical Studies In an in vivo study, ginger essential oil (GEO) exhibited hepatoprotective activity through its antioxidant potential against alcoholic fatty liver disease [141]. Lai et al. reported that GEO exhibited protective effect against NAFLD induced by high-fat diet in mice [142]. Recent studies also highlighted that ginger also shows hepatoprotective activity against diethyl-nitrosamine- and piroxicam-induced liver hepatotoxicity [143, 144].

2 Conclusions

It is a known fact that liver is the vital organ of the body and it performs a minimum of 500 functions. So, it is more liable to diseases. To cure these diseases, many chemically synthesized drugs are invented. But their usage causes uncountable side effects than improving the pathogenesis condition. To overcome all these detriments, there is a continuous demand for alternative therapy. One of the holistic approaches to treat liver diseases is the use of "natural medicine." Natural therapy for liver diseases is increasing worldwide, mainly because of their safety and efficacy, but also because of their relative expediency. Having said that, there is a great lack of comprehensiveness and huge controversies, regarding the safety and the mechanisms of action of these natural medicines. Having said that, it should not be taken by any means that the natural therapy does not have side effects. The most common side effects of using natural compounds include injury to liver, intestinal pneumonia, and acute respiratory failure, of which the licensed naturopathic doctors are aware. Although the natural medication is beneficial therapeutically, utmost care needs to be taken while treating the side effects. To prevent the complications arising due to the natural medicine, it is strongly advised that these medicines should be prescribed only by the licensed and certified physicians.

In this communication, we presented a few of such plants. Some of these plants and plant derivatives show good and satisfactory results in basic experimental and preclinical studies. However, more studies are required to evaluate the effects of these compounds before clinical use. So, we should take a step forward to develop these phytoconstituents into medicines. As prevention is always better than cure, we should include these plants and their products in diet. The two reasons, (1) often people thinking that natural medicines have no side effects and (2) lack of regulations to oversee the utilization of natural medicine, are the major concerns that often

lead to long-term and excess consumption of natural drugs that often bring undesirable reactions. Finally, both the doctor and the patient should be aware of the risks involved in taking the natural medicine and be careful while going for the natural therapy for liver diseases.

Conflict of Interest The authors declare no conflict of interest related to this book chapter.

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