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HEPATO ROTECTIVE ACTIVITY STUDIES ON HERBAL DRUG

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Abstract:

Liver is an essential organ. Its plays a main function in metabolism and excretion of xenobiotics from the body. Moreover it is also coping with the metabolism and excretion of medicine and other xenobiotics from the frame there with the aid of supplying safety towards foreign substances by using detoxifying agents and putting them off. The most important capabilities of the liver are carbohydrate, protein, fat metabolism and detoxification, secretion of bile and storage of vitamins. It plays an important role to maintaining various physiological processes in the body. It is involved in several vital functions, such as metabolism, excretion and storage. It plays a central role in the detoxification and excretion of many exogenous and endogenous compounds. Hence, any injury or impairment of its function has grave implications for the health of the affected person. Many more drugs or therapies are available for the treatment of hepatic disorders, but still there is a need for the novel drug discovery which can target multiple disease pathways.

Keywords: Plant extracts, Hepatotoxicity, Yakrit, Silybum marianum, Glycyrrhiza uralensis.

Introduction

Medicinal plants play a key role in the human health care. About 80% of the world population rely on the use of traditional medicine which is predominantly based on plant materials.[1] The traditional medicine refers to a broad range of ancient natural health care practices including folk/tribal practices as well as Ayurveda, Siddha, Amchi and Unani. These medical practices originated from time immemorial and developed gradually, to a large extent, by relying or based on practical experiences without significant references to modern scientific principles. [2] Liver is considered to be one of the most vital organs that functions as a centre of metabolism of nutrients such as carbohydrates, proteins and lipids and excretion of waste metabolites. Additionally, it is also handling the metabolism and excretion of drugs and other xenobiotic from the body thereby providing protection against foreign substances by detoxifying and eliminating them. [3] The bile secreted by the liver has, among other things, plays an important role in digestion. Liver cell injury caused by various toxicants such as certain chemotherapeutic agents, carbon tetrachloride-ride, thioacetamide etc., chronic alcohol consumption and microbes is well-studied. Enhanced

lipid peroxidation during metabolism of ethanol may result in development of hepatitis leading to cirrhosis. [4] It is estimated that about 7,500 plants are used in local health traditions in, mostly, rural and tribal villages of India. Out of these, the real medicinal value of over 4,000 plants is either little known or hitherto unknown to the mainstream population. The classical systems of medicine such as Ayurveda, Siddha, and Tibetan use about 1,200 plants. [5] A detailed investigation and documentation of plants used in local health traditions and pharmacological evaluation of these plants and their taxonomical relatives can lead to the development of invaluable plant drugs for many dreaded diseases. Random screening of plants has not proved economically effective. [6] The treatment options for common liver diseases are limited due to the lack of hepatoprotective drugs in allopathic medicine. In dealing with problems of the liver, the primary goal is to enhance liver detoxification processes and to help protect against further liver damage. Significant and safe hepato-protective agents are unavailable in modern therapeutics. Therefore, due importance has been given globally to develop plant-based hepato-protective drugs effective against a variety of liver disorders. [8]

More than 900 drugs & toxins have been reported to cause liver injury. [9] Though liver has its capacity to regenerate its tissues. The updated data confirmed that hepatotoxicity was the most commonly reported adverse drug reaction leading to drug withdrawal worldwide. Paradigm shift in search of hepatoprotectives drug moiety tracing back to ethno pharmacological background offers great scope. [10] This review article throws light upon hepatoprotectives used in Indian system of medicine.

Hepatoprotectives herbs

Herbal-based therapeutics for liver disorders has been in use in India for a long time and has been popularized world over by leading pharmaceuticals. [11] Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still unacceptable treatment modalities for liver dis-eases. The limiting factors that contribute to this eventuality are (i) lack of standardization of the herbal drugs; (ii) lack of identification of active ingredient(s)/principles(s); (iii) lack of randomized controlled clinical trials (RCTs), and (iv) lack of toxicological evaluation. The use of natural remedies for the treatment of liver diseases has a long history, starting with the Ayurveda treatment, and extending to the Chinese, European and other systems of traditional medicines[12]

Silybum marianum

The protective effects of polyphenolic extracts of *Sily-bum marianum* and *Cichorium intybus* on thioaceta-mide- induced hepatotoxicity in rat was investigated. [13] The extracts were injected to the rats, at a dose of 25 mg kg-1 body weight together with thioacetamide at a dose of 50 mg kg body weight. Sig-nificant decrease in the activity of aminotransferases, alkaline phosphatase and bilirubin was observed in the groups treated with extracts and thioacetamide com-pared with the group that was treated only with thioa-cetamide. [11]

Coccinia grandis

Alcoholic extract of the fruits of *Coccinia grandis* Linn (Curcubitaceae) was evaluated in CCl4- induced hepato-toxicity in rats and levels of AST, ALT, ALP, total proteins, total and direct bilirubin were evaluated. [15] At a dose level of 250 mg/kg, the alcoholic extract significantly ($p<0.05$) decreased the activities of serum en-zymes (AST, ALT and ALP) and bilirubin which were comparable to that of silymarin revealing its hepato-protective effect.

Ficus carica

The methanolic extract of the leaves of *Ficus carica* Linn. (Moraceae) was evaluated for hepatoprotective activity in CCl4 -induced liver damaged rats. The extract at an oral dose of 500 mg/kg exhibited a significant protective effect reflected by lowering the serum levels of AST, ALT, total serum bilirubin, and malondialdehyde equivalent, an index of lipid peroxidation of the liver. [16]

Lepidium sativum

The role hepato-protective of methanolic extract of *Lepidium sativum* at a dose of 200 and 400 mg/kg was investigated in CCl4-induced liver damage in rats. Sig-nificant reduction in all biochemical parameters were found in groups treated with *Lepidium sativum.* The severe fatty changes in the livers of rats caused by CCl4 were insignificant in the *Lepidium sativum* treated groups[17]

Aegle marmelos

Aegle marmelos leaves (*Bael*, family of Rutaceae) which is also called as *Bilva* in ancient Sanskrit, was used as herbal drug in the Indian System of medicine. The hepatoprotective effect of *Aegle marmelos* in al-cohol-induced liver injury was evaluated rats using es-sential marker biochemical parameters. [18] The results indicated that, the *Bael* leaves have excellent hepato-protective effect. Similar findings were also reported by other workers

Solanum nigrum

The effects of *Solanum nigrum* extract (SNE) was evaluated on thioacetamide (TAA)-induced liver fibrosis in mice. Mice in the three TAA groups were treated daily with distilled water and SNE (0.2 or 1.0 g/kg) via gastro gavage throughout the experimental period. SNE reduced the hepatic hydroxyproline and α -smooth muscle actin protein levels in TAA-treated mice. SNE inhibited TAA-induced collagen (α1)(I), transforming growth factor-β1 (TGF-β1) and mRNA levels in the liver. [19] Histological examination also confirmed that SNE reduced the degree of fibrosis caused by TAA treatment. Oral administration of SNE significantly reduces TAA-induced hepatic fibrosis in mice, probably through the reduction of TGF-β1 secretion

S. chinensis (Turcz.) Baill

S. chinensis (Turcz.) Baill is widely used in traditional and modern Chinese medicine for the treatment of many disorders including insomnia, respiratory failure, and weakness. Moreover, mental health improving ability along with fatigue reduction property is also validated for S. chinensis in Russian medicine. [20] In general, dibenzocyclooctadiene lignans found in S. chinensis are known to exhibit potent hepatoprotective activity. In one of the study of individual lignin, Gomisin A was found responsible for the acceleration of hepatocytes proliferation and increase hepatic flow . Furthermore, elevation of mitochondrial glutathione concentration was found to be linked with γ-schisandrin hepatoprotective mechanism. The increase in vitamin C concentration in the liver of test animals upon treatment with γ-schisandrin also validates its hepatoprotective ability. Another individual lignin, Schisandrin B was also found to counter oxidative harm to liver tissues. In one scientific study, the hepatoprotective mechanism against acetaminophen-induced liver injury of six Schisandra lignans (deoxyschisandrin, Schisantherin A, Schisandrin B, Gomisin A, Schisandrin C, and schisandrin) was elucidated. The hepatoprotective ability of these lignins was found to be associated with inhibition of cytochrome-mediated bioactivation[21]. Furthermore, another mechanistic study investigated the hepatoprotective effect of Schisandra polysaccharide in nonalcoholic fatty liver disease mice models. The results demonstrate potential down regulation of hepatic lipogenesis genes and LXRα/SREBP-1c/ FAS/ACC and SREBP-2/HMGCR signaling pathways in the liver

C. chinensis Lam.

C. chinensis Lam. also known as Chinese dodder is a parasitic plant having diverse traditional medicinal uses as a tonic, sex enhancer, and abortion preventer Studies also have scientifically validated the hepatoprotective activity of C. chinensis evaluated the hepatoprotective effect of C. chinensis ethanol solution extract in rats with the acetaminophen-induced toxicity of liver. The elevated concentration of glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, and alkaline phosphatase was reduced significantly via treatment of rats with 125 and 250 mg/kg of C. chinensis ethanol extract orally. [22] Furthermore, it was found that the ethanol solution extract prevented centribular hepatic necrosis and acetaminophen- induced toxicity of liver. The ethanol solution extract was further found to also elevate the level of potential antioxidant enzymes like glutathione peroxidase, superoxide dismutase, and catalase. [23] In another study by the same group, nanoparticles formulation of C. chinensis seeds ethanol solution extract was found to be more effective in rats with acetaminophen-induced hepatotoxicity. The mechanism of hepatoprotective potential as demonstrated by ethanol solution extract of C. chinensis is proposed to be the elevated activities of antioxidant enzymes. [24]

L. barbarum L

L. barbarum L. berries are very famous in traditional Chinese medicine for the treatment of inflammation, cancer, eye disorders, throat infection, and anemia. [25] The use of these berries has been validated as food and also has gained great importance due to its significant antioxidant potential. The major active components of L. barbarum berries are L.barbarum polysaccharides (LBPs) which are reported widely to

have diverse pharmacological properties. In a study, the hepatoprotective effect of LBPs in rats having alcohol-induced liver injury has been validated. Liver injury model was made via treatment of ethanol, which exhibited elevated levels of liver enzymes and fatty liver. Upon treatment of L. barbarum polysaccharides for 30 days in a dosage of 300 mg/kg, the liver injury model revealed prevention of fatty liver and minimized liver injury Diels A. sinensis (Oliv.) Diels is reported in Chinese herbal medicine for the treatment of cardiovascular disease, anemia, and hepatic disorders. [26] The A. sinensis polysaccharides (ASP) extracted from A. sinensis roots having the average molecular weight of 72,900 Da is regarded as a potential active component of A. sinensis that exhibits a wide range of pharmacognostic properties. The hepatoprotective potential of ASP in CCl4-induced liver injury and via using ischemia/reperfusion rat is widely established have investigated the hepatoprotectives mechanism of ASP against Concanavalin Ainduced failure of the liver. It was found that 5 to 125 μg/mL of ASP has inhibited the Concanavalin A-induced responses. Major reduction in the levels of serum transaminase was seen, whereas Hematoxylin and Eosin staining reported liver inflammation attenuation. The study concluded that pretreatment of ASP elicits antiinflammatory and antioxidant actions, which attenuates Concanavalin A-induced liver injury. In another study, Zhao et al., investigated the role of A. sinensis derived Levistilide A against CCl4-induced liver fibrosis. The results validated the potential role of Levistilide A in liver fibrosis inhibition via antiangiogenesis

Table no 1: Hepatoprotective medicinal plants with potential bioactive compounds and it's mechanism of actions

Plant	Part used	Potential agents	Mechanism of action
Amaranthus spinosus L.	Whole plant	Flavonoids and phenolic compounds	Enzymatic levels of serum glutamate, oxaloacetate transaminase (AST), serum glutamate pyruvate, transaminase (ALT), serum alkaline,phosphatase (SALP), and total, bilirubin were reinstated to the, normal level [27]
Calotropis procera (Aiton) Dryand.	Flowers	Crude hydro-ethanol solution extract	Prevents of the depletion of GSH levels. C. procera contains flavonoids thus it also performs the antioxidant activity [34]
Clerodendrum abilioi R. Fern.	Leaves	Crude ethanol solution extract	Ethanol extract decreased the serum enzyme ALT, AST, ALP, TGL, and total cholesterol and considerably increased the glutathione level [35]
Glycyrrhiza uralensis	Root	Glycyrrhizin	Glycyrrhizin administered in PLC/PRF/5 cells suppressed the secretion of HBsAg into the culture medium and concluded that glycyrrhizin modifies the Intracellular transport and the surface nature of the hepatocytes
Nelumbo nucifera Gaertn.	Leaves	Catechin glycoside, myricitrin-3-O-glucoside,hyperin, isoquercitrin, quercetin-3-O-rhamnoside, astragalin	Lotus leaf extract possess significant hepatoprotective and antioxidant activity in CCl4-induced toxicity rat model. Free radicalscavenging and antioxidant activity due to the presence of some flavonoids and phenolic compounds results in the hepatoprotective activity.
S. miltiorrhiza Bunge.	Roots	S. miltiorrhiza polysaccharides	Protects liver against immunological injury by adjusting the levels of alanine aminotransferase, aspartate minotransferase, nitric oxide, tumor necrosis factor and interleukin-1
nigrum L. and Cichorium intybus L.	Leaves	Crude plant extract	Protect DNA against oxidative damage in the reaction mixture containing calfthymus DNA and free radical generatingsystem [36]

Vitex negundo L.	Leaves	Crude ethanol solution extract	Administration of ethanol solution extract of Vitex leaf caused a significant decrease in TB, AST, ALT, and ALP levels in rats. [38]

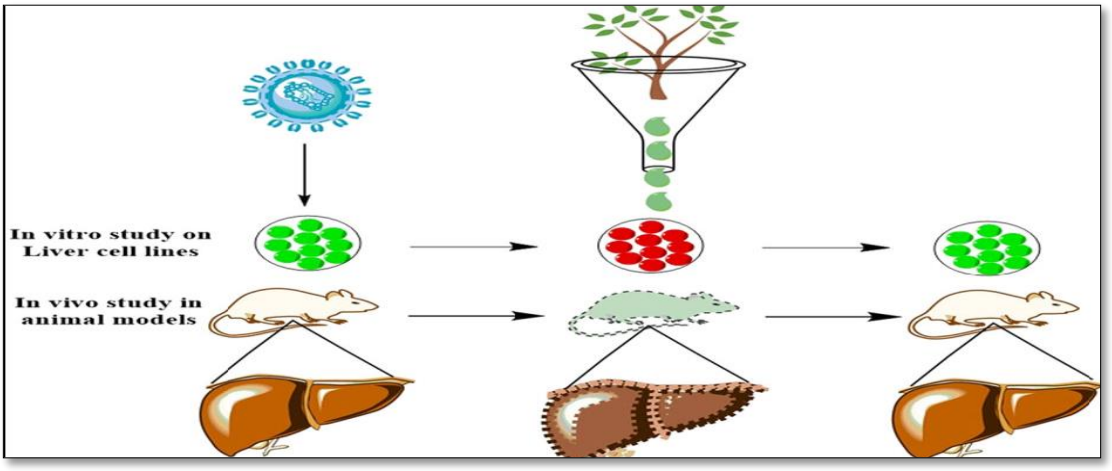

Figure no : 1. s in vitro and in vivo hepatoprotective activity of plant extracts in mice.

Methodology

A list of hepatoprotective plants used in Indian Arabia was prepared based on a nationwide survey of herbal drug used in traditional medicine for liver ailment by[28]

(a) interviewing the patients visiting primary care centers of military hospitals of different regions of Indian Arabia,

(b) review of traditional medicinal books/publications and folklore information. Thorough of survey of literature on the pharmacological profile of these plants was undertaken to collect the published data for the period between 1975 and 2014 AD by using "Pubmed" and "Google Scholar" search engines. [29] Attempt was made to determine if these plants have been tested for hepatoprotective activity using well-established experimental models including carbon tetrachloride (CCl4), thioacetamide, paracetamol, ethanol, and morphine induced liver damage.

The liver enzymes including aspartate transaminase (AST), [30] alanine transaminase (ALT), alkaline phosphatase (APT), total protein (TP), [31] and albumin (Alb) were used as a marker of liver injury. Literature search also included reversal of toxin induced histopathological changes by plant drugs. An attempt has been made to illustrate possible mechanism of hepatoprotective herbs with special reference to their antioxidant and inflammatory mediators. [32] Available data about the chemical constituent of the hepatoprotective plants and their toxicity has also been presented. Briefly, this review summarises the information about 35 hepatoprotective herbal drugs used in Indian traditional medicine for the treatment of liver diseases including their botanical name, family, and part of the plant used, distribution of plants in Indian Arabia, and their use in traditional medicine. [33]The results of hepatoprotective studies on each plant, possible mechanism of action, and their chemical composition and toxicity data have been presented.

CONCLUSIONS

Hepatoprotective plants clearly indicate that herbal drugs have an enormous potential for the treatment of liver diseases. In this article, we reviewed the scientific merit of selected plants studied for their hepatoprotectives mechanism of action. The major hepatoprotectives mechanism identified by the majority of the studies is through combating the oxidative stress that damages the liver therefore, we conclude that herbs and herbal preparations are among the most important sources of hepatoprotectives and liver regeneration medicines. However, further research is needed to identify, characterize, and standardize the active ingredients, useful compounds, and their preparations for the treatment of liver diseases. Moreover, a combination of the traditional herbal medicines with the modern and conventional medicine may be one of the best options for the treatment of liver disorders and other diseases and infections, soon.

Future Prospects

About 80% of the world's population fulfills their healthcare needs from medicinal plants. There has been a significant rise in using over the-counter medicinal plant products containing powerful medicinal drugs and are believed to have to produce progressive effects with reduced side effects. However, therapeutic failures or adverse effects have been observed in many cases as pharmacological mechanisms of the herbal mixtures / preparations are not well studied.

Reference

1. **Agarwal AK, Mehendale JK. Potentiation of carbon tetrachloride hepatotoxicity and lethality by chlordecone in female rats. Toxicology 1983; 26: 231-42.**
2. Bomzon, S. Shtukmaster, and P. Ljubuncic, “The effect of an aqueous extract of *Teucrium polium* on glutathione homeostasis in vitro: a possible mechanism of its hepatoprotectant action,” *Advances in Pharmacological Sciences*, vol. 2010, Article ID 938324, 7 pages, 2010.
3. **Boyer TD, Rouf SL. Acetaminophen induced hepatic necrosis and renal failure. Journal of American Medical Association 1971; 218: 440–51.**
4. C.-C. Hsieh, H.-L. Fang, and W.-C. Lina, “Inhibitory effect of *Solanum nigrum* on thioacetamide-induced liver fibrosis in mice,” *Journal of Ethnopharmacology*, vol. 119, no. 1, pp. 117–121, 2008.
5. **Cameron GR, Thomas JC, Karunarathe WAE. The pathogenesis of liver injury in carbon tetrachloride and thioacetamide poisoning. Journal of Pathology and Bacteria 1936; 41: 297-304.**
6. **Childs JF, Siegler EA. Compounds for control of orange decays. Science; 1945. p. 102-68.**
7. **Dawkins MJR. Carbon tetrachloride poisoning in the liver of the new born rat. Journal of Pathology and Bacteria 1963; 85: 189-196.**
8. **Fitzhugh OG and Nelson AA. Liver Tumors in Rats Fed Thiourea or Thioacetamide, Science 1948; 108: 626-628.**
9. GO Ajayi, TT Adeniyi, DO Babayemi. Hepato-protective & some haematological effects of Allium sativum & vit.C in lead exposed wistar rats. International Journal of Medicine & Medical sciences. 2009; 1(3):064-067.

10. H. Kalantari, H. Forouzandeh, M. E. Azemi, I. Rashidi, and M. Goudarzi, "Study of the protective effect of *Teucrium polium* L. extract on acetaminophen-induced hepatotoxicity in mice," *Iranian Journal of Pharmaceutical Research*, vol. 12, no. 1, pp. 123–129, 2013.
11. **Handa SS, Sharma A. Hepatoprotective activity of Andrographolide from Andrographis paniculata against carbon tetrachloride. Indian Journal of Medical Research 1990; 92: 276-92.**
12. J. Shakhanbeh and O. Atrouse, "*Teucrium polium* inhibits nerve conduction and carrageenan-induced inflammation in the rat skin," *Turkish Journal ofMedical Sciences*, vol. 31, no. 1, pp. 15– 21, 2001.
13. Jayaram S, Thyagarajan SP. Inhibition of HbsAg secretion from Alexander cell line by Phyllanthus amarus. Indian Journal of Pathol. Microbial. 1996; 39:211-15.
14. **Kapur V, Pillai KK, Hussain SZ, Balani DK. Hepatoprotective activity of Jigrine on liver damage caused by alcohol, carbon tetrachloride and paracetamol in rats. Indian Journal of Pharmacology 1994; 26: 35-40.**
15. Kodakandla Venkata Syamsundar, Bikram Singh, Raghunath Singh Thakur, Aktar Husain, Yoshnobu, Kiso *et al*. Anti-hepatotoxic principles of Phyllanthus niruri. Journal of Ethnopharmacology. 1985; 14(1):41-44.
16. Lee CD, Ott M, thyagarajan SP, Shafritz DA, Burk RD, Gupta S. *Phyllanthus amarus* down-regulates hepatitis B virus mRNA transcription and replication. European Journal of Clinical Investigation, doi:10.1046/j.1365- 2362.1996.410595.x 1996; 26:1069-1076.
17. **Low TY, Leow CK, Salto-Tellez M, Chung MC. A proteomic analysis of thioacetamide-induced hepatotoxicity and cirrhosis in rat livers. Proteomics 2004; 4: 3960–74.**
18. Mandal. Hepatoprotective and antioxidant activities of Smilax chinensis L.Root. Parmacologyonline. 2008; 2:529-535
19. **Manokaran S, Jaswanth A, Sengottuvelu S, Nandakumar J, Duraisamy R, Karthikreyan D, et al. Hepatoprotective activity of Avera lanata Linn. against paracetomol induced hepatotoxicity in rats. Research Journal of Pharma Technology 2008; 1(4): 398–440.**
20. **Mazer M, Perrone J. Acetaminophen-induced nephrotoxicity: pathophysiology, clinical manifestations and management. Journal of Medical Toxicology 2008; 4(1): 2–6.**
21. Ott M, Thyagarajan SP, Gupta S. *Phyllanthus amarus* suppresses hepatitis B virus by interrupting interactions between HBV enhancer I and cellular transcription factors. European Journal of Clinical Investigation, doi:10.1046/j.1365- 2362.1997.2020749.x. 1997; 27: 908-915.
22. R. S. Orfali, *Phytochemical and Biological Study of Tamarix nilotica Growing in Saudi Arabia*, King Saud University, 2005.
23. Ram, A., Mabalirajan, U., Das, M., Bhattacharya, I., Dinda, A. K., Gangal,S. V., & Ghosh, B. (2006). Glycyrrhizin alleviates experimental allergic asthma in mice. International Immunopharmacology, 6(9), 1468–1477.
24. Rani, A., & Sharma, A. (2013). The genus Vitex: A review. Pharmacognosy Reviews, 7(14), 188–198.
25. Rastogi, R. P., & MB (1999). Compendium of Indian medicinal plants. CDRIPublication: New Delhi, 2, 609–610.

26. Rodrigues, N., Almeida, A., Silva, H., Pinto, D., Seca, A., Pereira, M. (2016). Potential anti-inflammatory effects of Artemisia gorgonum on rat liver injury induced by CCl4–ERRATUM. Microscopy and microanalysis: The official journal of Microscopy Society of America, Microbeam Analysis Society, Microscopical Society of Canada: 1–2.
27. S. Shenoy, K. Shwetha, K. Prabhu, R. Maradi, K. L. Bairy, and T. Shanbhag, "Evaluation of antiinflammatory activity of *Tephrosia purpurea* in rats," *Asian Pacific Journal of Tropical Medicine*, vol. 3, no. 3, pp. 193–195, 2010.
28. Shirwaiker A, Sreenivasan KK, Krishnanand BR, Kumar AV. Chemical investigation and anti hepatotoxic activity of the root bark of Caparis spinos. Fitoterapia 1996; 67: 200-204.
29. Sivasankari, B., Anandharaj, M., & Gunasekaran, P. (2014). An ethnobotanical study of indigenous knowledge on medicinal plants used by the village peoples of Thoppampatti, Dindigul district, Tamilnadu, India. Journal of Ethnopharmacology, 153(2), 408–423.
30. Son, Y. O., Kim, J., Lim, J. C., Chung, Y., Chung, G. H., & Lee, J. C. (2003). Ripe fruit of Solanum nigrum L. inhibits cell growth and induces apoptosis in MCF-7 cells. Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association, 41(10), 1421–1428.
31. SP Thyagarajan, S Jayaram, V Gopalakrishnan, R Hari, P Jeyakumar, V Gopalakrishnan *et al*. Herbal medicines for Liver Diseases in India. Journal of Gastroenterology & Hepatology. 2002; 17:s370-s376.
32. Stickel, F., Patsenker, E., & Schuppan, D. (2005). Herbal hepatotoxicity. Journal of Hepatology, 43(5), 901–910.
33. Street, R., Sidana, J., & Prinsloo, G. (2013). Cichorium intybus: Traditional uses, Phytochemistry, pharmacology, and toxicology. Evidence-based Complementary and Alternative Medicine, 2013, 13.
34. Suhagia, B., Rathod, I., & Sindhu, S. (2011). Sapindus mukorossi (Areetha): an overview. International Journal of Pharmaceutical Sciences and Research, 2(8), 1905.
35. Suja, S. R., Latha, P. G., Pushpangadan, P., & Rajasekharan, S. (2004). Evaluation of hepatoprotective effects of Helminthostachys zeylanica (L.) Hook against carbon tetrachloride-induced liver damage in Wistar rats. Journal of Ethnopharmacology, 92(1), 61–66.
36. T. Hussain, S. Fareed, H. H. Siddiqui, M. Vijaykumar, and C. V. Rao, "Acute and subacute oral toxicity evaluation of *Tephrosia purpurea* extract in rodents," *Asian Pacific Journal of Tropical Disease*, vol. 2, no. 2, pp. 129–132, 2012.
37. Taranalli, AD., Kuppast, IJ., Study of wound healing activity of seeds of Trigonella foenum-graecum in rats. Ind. J. Pharm. Sci 1996; 58: 117–119.
38. U. S. Akula and B. Odhav, "In vitro 5-lipoxygenase inhibition of polyphenolic antioxidants fromundomesticated plants of South Africa," *Journal of Medicinal Plants Research*, vol. 2, no. 9, pp. 207–212, 2008.
39. V Vimal, T Devaki. Hepato-protective effect of allicin on defense system in galactosamine/endotoxin challenged rats, Journal of ethnopharmacology, 2004.
40. Venkidesh R. Hepatoprotective activity of Smilax chinensis L.in CCl4 induced hepatotoxicity in rats.International Journal of Biological & Pharmaceutical Research. 2010; 1(2):72-75.

41. X.-F. Cai, Y.-W. Chin, S.-R. Oh, O.-K. Kwon, K.-S. Ahn, and H.- K. Lee, "Anti-inflammatory constituents from*Solanumnigrum*," *Bulletin of theKoreanChemical Society*, vol. 31,no. 1, pp. 199–201, 2010.
42. Yen, F.-L., Wu, T.-H., Lin, L.-T., & Lin, C.-C. (2007). Hepatoprotective andantioxidant effects of Cuscuta chinensis against acetaminopheninduced hepatotoxicity in rats. Journal of Ethnopharmacology, 111(1), 123–128.
43. Yin, H. Q., Choi, Y. J., Kim, Y. C., Sohn, D. H., Ryu, S. Y., & Lee, B. H. (2009).Salvia miltiorrhiza Bunge and its active component cryptotanshinone protects primary cultured rat hepatocytes from acute ethanol-induced cytotoxicity and fatty infiltration. Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association, 47(1), 98–103.
44. Yip, P. Y., & Kwan, H. S. (2006). Molecular identification of Astragalus membranaceus at the species and locality levels. Journal of Ethnopharmacology, 106(2), 222–229.
45. **Zargar S. Protective effect of Trigonella foenum-graecum on thioacetamide induced hepatotoxicity in rats. Saudi Journal of Biological Sciences 1994; 2: 139–145.**
46. Zein, N. N., Rakela, J., Krawitt, E. L., Reddy, K. R., Tominaga, T., & Persing, D.H. (1996). Hepatitis C virus genotypes in the United States: Epidemiology,pathogenicity, and response to interferon therapy. Collaborative study group. Annals of Internal Medicine, 125(8), 634–639.
47. Zhang, J., Xie, X., Li, C., & Fu, P. (2009). Systematic review of the renal protective effect of Astragalus membranaceus (root) on diabetic nephropathy in animal models. Journal of Ethnopharmacology, 126(2), 189–196.
48. Zhang, S., He, B., Ge, J., Li, H., Luo, X., Zhang, H., … Fei, X. (2010). Extraction, chemical analysis of Angelica sinensis polysaccharides and antioxidant activity of the polysaccharides in ischemia–reperfusion rats. International Journal of Biological Macromolecules, 47(4), 546–550.
49. Zhao, Z. M., Liu, H. L., Sun, X., Guo, T., Shen, L., Tao, Y. Y., & Liu, C. H. (2017). Levistilide A inhibits angiogenesis in liver fibrosis via vascular endothelial growth factor signaling pathway. Experimental Biology and Medicine, 242(9), 974–985.
50. Zheng, C. J., Li, H. Q., Ren, S. C., Xu, C. L., Rahman, K., Qin, L. P., & Sun, Y. H. (2015). Phytochemical and pharmacological profile of Vitex negundo. Phytotherapy research : PTR, 29(5), 633–647.
51. Zheng, H., Dong, Z., & She, J. (1998). Modern study of traditional Chinese medicine. Xue Yuan Press Beijing China, 3, 2057.
52. **Zimmerman MD, Hayman J. Function and integrity of the liver. In: Richard A McPherson, Matthew R Pincus, and John Bernard Henry. Clinical diagnosis and management by laboratory methods. Edition 17, Saunders Elsevier, New York; 1976. p. 217-50.**