Available Online at www.ijpscr.info
International Journal of Pharmaceutical Sciences and Clinical Research 2023; 3(2):60-66

REVIEW ARTICLE

Recent Advancement of Herbal Drug on Liver Disorder

Kanhaiyalal Kumawat[1], Bharat Chouhan[2]

[1,2]*Department of B. Pharmacy, B.R. Nahata College of Pharmacy, Mandsaur University, Mandsaur (M.P.), 458001, India*

Received: 07-03-2023 Revised: 26-03-2023 Accepted: 18-04-2023

ABSTRACT

Hepatotoxicity damage is a common complication because the liver has to detoxicate many toxic substances. Most of the hepatotoxic chemicals damage cells primarily by producing reactive species which from covalent bond the lipids of the tissue due to excessive exposure hazardous chemicals like carbon tetrachloride, alcohol thioacetamide etc. Medicinal plants play a key role in human health care. About 80% of the world population believes in the use of traditional medicine which is based on plant materials. This review article is based on the recent advancement of herbal drug for liver disorder.

Keywords: Hepatotoxicity, Herbal drugs, Liver disorder

INTRODUCTION

The liver is the largest gland in the body, weighing between 1 and 2.3 kg. It is situated in the upper part of the abdominal cavity occupying the greater part of the right hypochondriac region, part of the epigastric region, and extending into the left hypochondriac region. The liver has many functions any other human organ.[1] In human entire blood supply passes through several times a day, the liver has a vital role in human metabolism, liver produces and secretes bile, it also produces prothrombin and fibrinogen, both blood clotting and heparin, a mucopolysaccharide sulfuric acid ester that helps to keep blood from clotting within the circulatory system. The liver has the major role in the conversion of sugar into glycogen.[1]

Treatment options for common liver diseases such as cirrhosis, fatty liver, and chronic hepatitis are often limited in efficacy, carry the risk of adverse effect, and are often too costly, especially for the developing world. Hepatotoxicity due to drugs appears most common contributing factor. Liver damage is a common complication because the liver has to detoxicate many toxic substances. Most of the hepatotoxic chemicals damage cells primarily by producing reactive species which from covalent bond the lipids of the tissue due to excessive exposure hazardous chemicals like carbon tetrachloride, alcohol thioacetamide etc.

Medicinal plants play a key role in human health care. About 80% of the world population beliefs on the use of traditional medicine which is based on plant materials. The traditional medicine refers to a wide range of ancient natural healthcare practices including folk and tribal practices as well as Ayurveda, siddha, and Unani it is estimated that about 7500 plants are used therapeutically mostly rural and tribal villages of India. The classical system of medicines such as Ayurveda, Siddha, Amchi, Unani, and Tibetan use about 1200 plants.[2] Scientific evaluation of plants has often shown that active principles in these are responsible for therapeutic success. A large number of medicinal plants have been tested and found to contains active principles with preventive against off variety of diseases. Hepatoprotective plants possess

***Corresponding Author:**
Kanhaiyalal Kumawat,
E-mail: kanhaiyalalkumawat8349@gmail.com

opulent chemical constituents such as silymarin, phyllanthin, and glycyrhizin curcumin.

Recent experience has shown that plant drugs are relatively non-toxic safe and even free from serious side effects. There is also concern with respect numerous well estabilized interactions of herbs and drugs in consultation with physician, usage of herbal remedies should be clarified. Some herbal remedies have the potential to cause adverse interactions when used in combination with various prescriptions and over the counter pharmaceuticals many consumer believe that herbal medicines are safe because they are natural. This review article focused on therapeutic potential of medicinal plants have hepatoprotective properties.[3]

HEPATOTOXICITY

Most often, hepatic injury is initiated by the bioactivation of drugs to chemically reactive metabolites which interact with cellular macromolecules such as proteins, lipids, and nucleic acids, leading to protein dysfunction, lipid peroxidation, DNA damage, and oxidative stress. In addition, these reactive metabolites may stimulate the disruption of ionic gradients and intracellular calcium stores, which result in mitochondrial dysfunction and loss of energy production. Activation of some cytochrome P450 enzymes, for example, CYP2E1 also cause oxidative stress.[4] The accumulation of bile acid in the liver due to injury to the liver and bile duct cells, can promote further liver damage. The culmination of this imbalance in cellular activity can lead to cell death and ultimately liver failure. Hepatocyte dysfunction can lead to immunological responses. Signals that encourage the activation of other cells, notably those of the innate immune repertoire, such as kupffer cells, natural killer cells, and natural killer T-cells, are released in response to stress and hepatic injury. By generating pro-inflammatory mediators and secreting chemokines to further entice inflammatory cells to the liver, these cells facilitate the course of liver injury.

It has been demonstrated that inflammatory cytokines released after hepatic injury, such as tumor necrosis factor (TNF), interferon (IFN), and interleukin (IL)-1, actively encourage tissue damage. In contrast, the main source of IL-10, IL-6, and certain prostaglandins, all of which have hepatoprotective properties, is innate immune cells.[5]

PHYTOCONSTITUENTS WITH HEPATOPROTECTIVE POTENTIALS

Silymarin[6]

Chemical formula -$C_{25}H$ [Figure 5]

- Synonyms - Milk thistle, marian thistle, mary thistle
- *Biological source* - it is extracted from the seed and fruits of *Silybum marianum* (milk thistle) [Figure 2]
- *Familly* - Compositae
- *Phytoconstituents* - silybin or silybinin, silydianin and silychristin
- *Uses* – hepatoprotection, antiinflammation, antioxidation, antifibrotic activity.

All of the isomers, that constitute silymarin, silybin is the most active [Figure 1]. Silymarin and silybin have been found to provide cytoprotection and above all, hepatoprotection. Silymarin has been found to cureb zvarious liver disorders as it has established the efficacy in restoration of liver function and regenartion of liver cells.

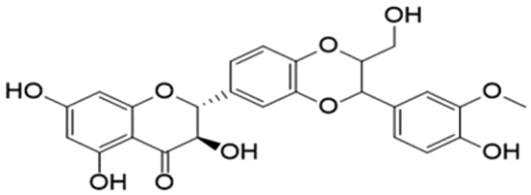

Figure 1: Chemical structure[7]

Figure 2: Milkthistle[8]

Machanism of action of silymarin[4]

As a hepatoprotective drug, silymarin has been reported to possess multiple mechanism of actions against different hepatotoxic agents.[5] The antioxidant property and cell regenerating functions as a result of increased protein synthesis are considered as most important As a hepatoprotective drug, silymarin has been reported to possess multiple mechanism of actions against different hepatotoxic agents The antioxidant property and cell regenerating functions as a result of increased protein synthesis are considered as most important actions. Silymarin or *S. marianum* has the antioxidant activity Free radicals, including superoxide radical, marianum has the antioxidant activity. Free radicals, including superoxide radical hydroxyl radical hydrogen peroxide and lipid peroxide radicals have been implicated in liver diseases.

These reactive oxygen species (ROS) are produced as a normal consequence of biochemical processes in the body and as a result of increased exposure to xenobiotics. The mechanism of free radical damage include ROS induced peroxidation of polyunsaturated fatty acid in the cell membrane bilayer, which causes a chain reaction of lipid peroxidation, thus damaging the cellular membrane and causing further oxidation of membrane lipids and proteins. Subsequently cell contents, including DNA, RNA and other cellular components are damaged.

The cytoprotective effects of silymarin are mainly attributable to its antioxidant and free radical scavenging properties. Silymarin can also interact directly with cell membrane components to prevent any abnormalities in the content of lipid fraction responsible for maintaining normal fluidity.[3] The stimulation of protein synthesis is an important step in the repair of hepatic injury, and is essential for restoring the structural proteins and enzymes damaged by hepatotoxins.

Overall, the hepatoprotection provided by silymarin appears to rest on four actions

(a) activity against lipid peroxidation as a result of free radical scavenging and the ability to increase the cellular content of GSH; (b) ability to regulate the membranepermeability and to increase membrane stability in the presence of xenobiotic damage; (c) capacity to regulate the nuclear expression by means of a steroid-like effect; and (d) inhibition of the transformation of stellate hepatocytes into myofibroblasts, which are collagen fibers leading to cirrhosis.

Silybinin probably acts not only on the cell membrane, but also on the nucleus, where it appeared to increase ribosomal protein synthesis by stimulating RNA works by acting as an antioxidant that prevents chainrupture.

Silybinin significantly increased the creation of ribosomes and DNA synthesis in addition to protein synthesis in *in vivo* and *in vitro* experiments conducted in the liver of rats from which part of the organ had been removed. The hepatic cytochrome P450 (CYP) detoxification system (phase I metabolism) can be inhibited by silymarin. Recently, it was demonstrated in mice that silybinin can block a variety of hepatic CYP enzyme activity. This effect could explain some of the hepatoprotective activities of silymarin, especially against the intoxicationdue to *Amanita phalloides*.

Glycyrrhizin[9]

Chemical formula – $C_{42}H_{62}O_{16}$

- Synonyms - Glycyrrizin, Liquorice, licorice, *Glycyrrhiza glabra*.
- Biological source - Glycyrrhizin is a plant glycoside extracted from roots of the liquorice plant (*G. glabra*) [Figure 4].
- Family - *Fabaceae*.
- Phytoconstituents - glycyrrhetinic acid (GA), flavonoids, hydroxyl coumarins, and b-sitosterol, isoliquiritin.
- Uses - hepatoprotective effect, anti- ulcer, anti- obesity, anti- diabetics etc.

Glycyrrhizin is the major active constituent of licorice root and has been used in traditional medicine to alleviate bronchitis, gastritis, and jaundice [Figure 3]. The major constituents are GA, flavonoids, hydroxyl coumarins, and b-sitosterol. It is a triterpene glycoside with GA that possesses a wide range of pharmacological and biological

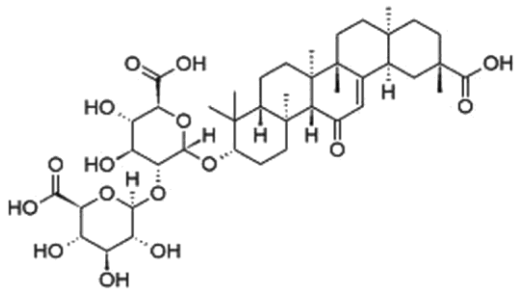

Figure 3: Chemical structure[10]

Figure 4: (a-c) Liquorice[11]

activities. When extracted from the plant, it can be obtained in the form of ammonium glycyrrhizin and mono-ammonium glycyrrhizin. Glycyrrhizic acid has been developed in Japan and China as a hepatoprotective drug in cases of chronic hepatitis. From January 2014, glycyrrhizic acid as part of the licorice extract was approved by the FDA as an existing food sweetener.

Mechanisms of GA

Inhibition of Hepatic Apoptosis and Necrosis - TNF-alpha is an important cytokine, which is a key mediator of hepatic apoptosis and necrosis in lipopolysaccharide/D-GaAlN-induced liver failure.[6] Plasma TNF level is also elevated in patients with chronic hepatitis caused by hepatitis B viral and acute alcoholic hepatitis. Therefore, TNF plays a key role in the pathogenesis of not only endotoxin-induced experimental liver injury but also many human liver diseases.

Some observations suggest that broad anti-inflammatory activity of GA is mediated by interaction with the lipid bilayer, thereby attenuating receptor mediated signaling[3] GA inhibited the lytic pathway of the complement system and may prevent tissue injury caused by the membrane attack complex. Therefore, GA could be a potent agent for suppressing complement-dependent tissue injury in autoimmune and inflammatory diseases.

Phyllanthin[12]

Chemical formula - $C_{24}H_{34}O_6$

- Biological source – It is obtained from *Phyllanthus amarus* [Figure 6]
- Family - *Euphorbiaceae*
- Phytoconstituents - alkaloids, astragalin, brevifolin, ellagitannins, amariin, repandusinic acid, phyllanthusiin D gallocatechins, geraniin, hypophyllanthin, lignans, lintetralins, lupeols, nirurin, phyllanthin, phyllanthine and phyllanthenol. Phyllanthin and hypophyllanthin
- Uses - antiseptic, diuretic, antiviral, anti-diabetic, hypotensive and antipyretic, hepatoprotective effect.

Mechanism of action of phyllanthin

The hepatoprotective effect of *P. amarus* has been confirmed by numerous studies that show the extract significantly restores the normal function of the liver cells, enzymes, and other indicators. In female mice, carbon tetrachloride (CCl4) administration resulted in a significant increase in liver and serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, and acid phosphatase (ACP), while total protein content significantly decreased. Krithika and Verma determined the hepatoprotective activity of *P. amarus* extract against CCl4-

Curcumin[15]

Chemical structure - $C_{21}H_{20}O_6$ [Figure 7]

- Synonyms - turmeric yellow, kurkum, haldi, Indian saffron
- Biological source - it is extracted from the rhizomes of *Curcuma longa* (turmeric) plant [Figure 8]
- Family - *Zingiberaceae*
- Phytoconstituents - Curcumin, demethoxycurcuminand,bisdemethoxycurcumin collectively known as curcuminoids
- Uses - Anti-inflammatory, Antioxidant, Anti-tumor, anti-cancer Anti- bacterial, anti-fungal, antiprotozoal.

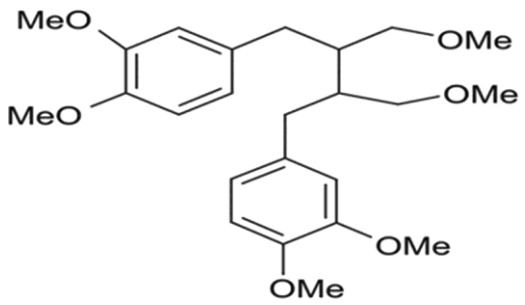

Figure 5: Chemical structure of phyllanthin[13]

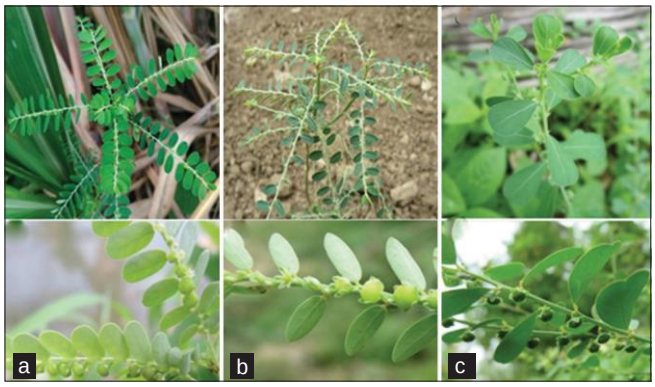

Figure 6: (a-c) *Phyllanthus amarus*[14]

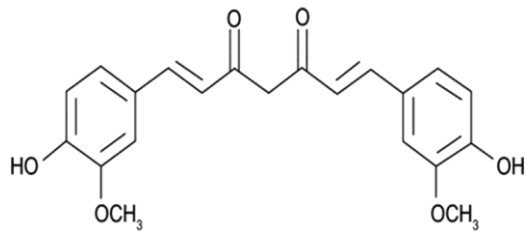

Figure 7: Chemical structure of curcumin[16]

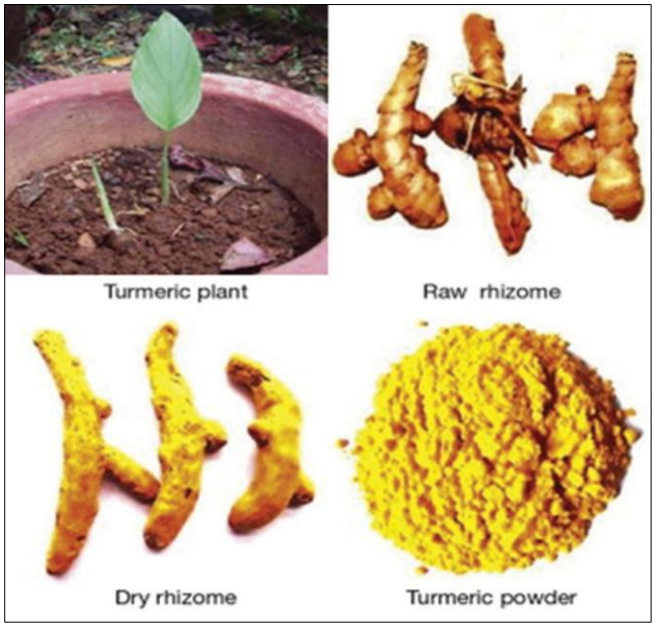

Figure 8: Turmeric[17]

Mechanism of action of curcumin

Curcumin and Hepatotoxicity -

In terms of drug toxicity, the liver is often the targeted organ. The production of ROS and RNS as the primary events, mitochondrial dysfunction and lipid dysmetabolism as the principal mechanisms of drug toxicity can be mentioned.[8]

The main problem with these medications is the usage of high doses, which usually lead to hepatotoxicity in humans and experimental animals.

CURRENT CLINICAL STATUS OF SOME HEPATOPROTECTIVE MEDICINES

Many herbal preparations which demonstrated significant hepatoprotective activity in preclinical studies have been successfully evaluated in clinical studies on patients suffering from dysfunctional hepatic system. To determine the effect of silymarin on the outcome of patients with cirrhosis, a double blind, prospective, randomized study was performed in 170 patients with cirrhosis. 87 patients received 140 mg silymarin 3 times daily whereas 83 received placebo. All patients received the treatment for 2 years. The 4-year survival rate was 58% in silymarin-treated patients and 39% in the placebo group indicating effectiveness of silymarin treatment.[20]

In a 6-month double blind clinical trial the effects of silymarin therapy on liver function tests, serum procollagen III peptide level and liver histology was studied in 36 patients with chronic alcoholic liver disease.[20] During silymarin treatment serum bilirubin, ALT and AST values normalized, while procollagen III peptide level decreased. The histological alterations showed an improvement in the silymarin group, while remained unchanged in the placebo group. These results indicated that silymarin improves liver functions in alcoholic patients.

The intervention consisted of daily administration of 140 mg of silymarin. There was a reduction in indirect bilirubin among those assigned to silymarin.

Efforts have been made to study the effect of silymarin treatment in patients with chronic hepatitis C. These results suggest that silymarin

may have a protective effect in the inflammatory response to HCV.

To validate the claims of Liv-52 being a potent hepatoprotective several clinical studies have been conducted. The efficacy of Liv-52 was determined on liver cirrhotic patients, a randomized, double blind, and placebo-controlled study was conducted in 36 cirrhotic patients in Tehran Hepatic Center. The efficacy of Liv-52 on liver cirrhosis outcomes was compared with the placebo for 6 months which are listed in Table 1.[21]

Results of this study conclude that Liv-52 possess hepatoprotective effect in cirrhotic patients In one retrospective study, effect of Liv-52 on 19 patients with alcoholic liver damage was investigated. It was found that administration of Liv-52 improved the subjective condition and clinical parameters in patients with liver damage. No undesirable side-effects were detected even after 1 year of treatment. The effectiveness of *P. amarus* in treatment of hepatitis has been demonstrated in a randomized study where 35 patients with chronic viral hepatitis B were treated with *P. amarus* derivative for 3 months in the treatment group while another 25 patients were treated with recombinant human IFNα-1b for 3 months as control. Effective rate in the treatment group was 83.3%. The normalization rates of ALT and bilirubin in the treatment group were significantly higher than that in the control. The negative conversion rates of HBeAg and HBV-DNA in the treatment group were 42.3% and 47.8%, showing no significant difference from the control.[22]

It is indicated that *P. amarus* derivative has remarkable effect for chronic viral hepatitis B in recovery of liver function and inhibition of the replication of HBV.[22] There are several herbal preparations which are used as hepatoprotective drugs worldwide, some of which are listed in Table 2.

Table 1: List of lead molecules with hepatoprotective activity[18]

Isolated lead	Family	Hepatoprotective activity
Asiaticoside	*Centella asiatica*	Lipopolysaccharide/d-galactosamine induced
Cleomiscosins	*Cleome viscosa*	CCl4-induced; thioacetamide induced
Puerarin	*Pueraria lobata*	CCl4-induced
Celosin A (1) and celosin B (2)	*Semen celosiae*	CCl4-induced
α- and β-amyrin	*Protium heptaphyllum*	Paracetamol induced
Rubiadin	*Rubia cordifolia*	CCl4-induced
Dehydrocavidine	*Corydalis saxicola*	CCl4-induced
Wedelolactone	*Eclipta alba*	CCl4-induced
Cichotyboside	*Cichorium intybus*	CCl4-induced

Table 2: List of herbal preparations available as hepatoprotective drugs[19]

Herbal preparations	Names of plants	Major constituents	Therapeutic indications
Legalon	*Silybum marianum*	Silymarin	Liver disorders, liver cirrhosis
Liv-52	*Capparis spinosa, C intybus, S. nigrum, Terminalia arjuna, Cassia occidentalis, Achillea millefolium, Tamarix gallica*	Solasodine, inulin, cichoriin, arjunolic acid, arjunine, chamazulene, tamarixin, stachydrine, achilline	Jaundice, Alcoholic liver disease, Viral hepatitis.
Hepatomed	*P. kurroa, A.paniculata, Eclipta alba, C. intybus, S. nigrum, Phyllanthus niruri*	Andrographolide, picroside, phyllanthin, hypophyllanthin, wedelolactone	Jaundice, Alcoholic liver disease, cirrhotic liver disease
HD 03	*C. intybus, S. nigrum, P. kurroa, A. paniculata, T. purpurea*	Solasodine, inulin, cichoriin, picroside, tephrosin, andrographolide	Jaundice, Alcoholic liver disease, Viral hepatitis
Kamilari	*Thespesia populnea, Elettaria cardamomum, Zingiber officinale.*	Populneol, cineole, glycyrrhizin, zingerone, gingerols	Jaundice, Alcoholic liverdisease,Viral hepatitis, liver cirrhosis
Livfit	*E. alba, P. niruri, C. intybus, Rheum emodi, T. purpurea*	Wedelolactone, phyllanthin, emodin, aloe-emodin, rhein, tephrosin	Protects liver against various hepatotoxins
Stimuliv	*A. paniculata, P. niruri, E. alba, P. kurroa, Boerhaavia diffusa, Azadirachta indica, Berberis aristata, Ipomoea turpethum, T. purpurea*	Punarnavoside, liirodendrin, picroside, berberine, nimbin, nimbinin	Liver stimulant and tonic
Himoliv	*P. kurroa, B. diffusa, Tinospora cordifolia, A. paniculata, Phyllanthus emblica*	Tinsporine, tinosporide	Ayurvedic medicine for hepatic dysfunction

C. intybus: Cichorium intybus, S. nigrum: Solanum nigrum, P. niruri: Phyllanthus niruri, T. purpurea: Tephrosia purpurea, A. paniculata: Andrographis paniculata, P. kurroa: Picrorhiza kurroa

CONCLUSION

Herbal medicines derived from plant extracts are being increasingly utilized to treat a wide variety of clinical diseases, with large efforts being made to elucidate their modes of action. Large sections of patients with liver disease use botanicals. Future efforts will have to implement extensive methodological improvements to separate the real therapeutic value of these agents from unsubstantiated hopes associated with them. The active molecules must be isolated and tested through well designed experiments and finally in randomized, placebo-controlled studies to enable rational clinical use of the agents. There is a huge demand for both experimental and clinical research to validate the potential of herbal drugs and rigorous scientific testing along the principles of evidence-based medicine will help herbal medicine to become a very justifiable scientific treatment regime.

REFERENCES

1. Waugh A, Grant A. Ross and Wilson Textbook of Anatomy and Physiology in Health and Illness. 5th ed. Amsterdam: Elsevier-Health Sciences Division; 2010.
2. Maity T, Maity S, Pahari N, Kar DJ, Ganguli S. A review on hepatic diseases and development of herbal drugs for the treatment of liver complications. World J Pharm Res 2015;4:677-91.
3. Ghosh N, Ghosh R, Mandel V, Mandal SC. Recent advances in herbal medicine for treatment of liver diseases. Pharm Biol 2011;49:970-88.
4. Farzaei MH, Zobeiri M, Parvizi F, El-Senduny FF, Marmouzi I, Coy-Barrera E. Curcumin in liver diseases: A systematic review of the cellular mechanisms of oxidative stress and clinical perspective. Nutrients 2018;10:855.
5. Govind P, Sahni YP. A review on hepatoprotective activity of silymarin. Int J Res Ayurveda Pharm 2011;2:75-9.
6. Li JY, Cao HY, Liu P, Cheng GH, Sun MY. Glycyrrhizic acid in the treatment of liver diseases: Literature review. Biomed Res Int 2014;2014:872139.
7. Hasssan MA, Masud IA. An overview of the Hepatoprotective potentials of *Phyllanthus amarus*. J Pharmacogn Phytochem 2018;7:2777-82.
8. Hegde K, Haniadka R, Alva A, Periera-Colaco MM, Baliga S. Turmeric (*Curcuma longa* L.) the golden curry spice as a nontoxic gastroprotective agent. In: Bioactive Food as Dietary Interventions for Liver and Gastrointestinal Disease. Amsterdam: Elsevier Inc.; 2013. p. 337-48.
9. Niranjan A, Prakash D. Chemical constituents and biological activities of turmeric (*Curcuma longa* L.)-a review. J Food Sci Technol 2008;45:109-16.
10. Gupta NK, Dixit VK. Evaluation of hepatoprotective activity of *Cleome viscosa* Linn. Extract. Indian J Pharmacol 2009;41:36-40.
11. Sun ZL, Wang Y, Guo ML, Li YX. Two new hepaprotective saponins from *Semen celosiae*. Fitoterapia 2010;81:375-80.
12. Oliveira FA, Chaves MH, Almeida FR, Lima RC Jr., Silva RM, Maia JL, *et al*. Protective effect of alpha- and beta-amyrin, a triterpene mixture from *Protium heptaphyllum* (Aubl.) March. Trunk wood resin, against acetaminophen-induced liver injury in mice. J Ethnopharmacol 2005;98:103-8.
13. Singh B, Saxena AK, Chandan BK, Agarwal SG, Anand KK. *In vivo* hepatoprotective activity of active fraction from ethanolic extract of *Eclipta alba* leaves. Indian J Physiol Pharmacol 2001;45:435-41.
14. Ahmed B, Khan S, Masood MH, Siddique AH. Anti-hepatotoxic activity of cichotyboside, a sesquiterpene glycoside from the seeds of *Cichorium intybus*. J Asian Nat Prod Res 2008;10:223-31.
15. Torres M, Rodríguez-Serrano F, Rosario DJ, Rodríguez-Perez F, Toro DH. Does *Silybum marianum* play a role in the treatment of chronic hepatitis C? P R Health Sci J 2004;23:69-74.
16. Kaláb M, Krechler T. The effect of the heptoprotective agent LIV 52 on liver damage. Cas Lek Cesk 1997;136:758-60.
17. Mayer KE, Myers RP, Lee SS. Silymarin treatment of viral hepatitis: A systematic review. J Viral Hepat 2005;12:559-67.
18. Mitra SK, Venkataranganna MV, Sundaram R, Gopumadhavan S. Protective effect of HD-03, a herbal formulation, against various hepatotoxic agents in rats. J Ethnopharmacol 1998;63:181-6.
19. Rajesh MG, Latha MS. Preliminary evaluation of the antihepatotoxic activity of Kamilari, a polyherbal formulation. J Ethnopharmacol 2004;91:99-104.
20. Gupta YK, Sharma M, Chaudhary G, Katiyar CK. Hepatoprotective effect of new livfit, a polyherbal formulation, is mediated through its free radical scavenging activity. Phytother Res 2004;18:362-4.
21. Dange SV, Shah KU, Bulakh PM, Joshi DR. Efficacy of stimuliv, an indigenous compound formulation, against hepatotoxicity of antitubercular drugs--a double blind study. Indian J Chest Dis Allied Sci 1992;34:175-83.
22. Bhattacharyya D, Pandit S, Mukherjee R, Das N, Sur TK. Hepatoprotective effect of himoliv, a polyherbal formulation in rats. Indian J Physiol Pharmacol 2003;47:435-40.