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HERBAL HEPATOPROTECTIVE AGENTS: A REVIEW

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ABSTRACT

Medicinal plants are significant source of Hepatoprotective drugs. Mono and poly-herbal preparations have been used in various liver disorders since ages. According to one estimate, more than 700 mono and poly-herbal preparations in the form of decoction, tincture, tablets and capsules from more than 100 plants are in clinical use. A drug having beneficial effect on the liver is known as Hepatoprotective drug. On the other hand, drugs having toxic affect on the liver are better known as hepatotoxic drugs. Clinical research has also shown that herbals have genuine utility in the treatment of liver diseases. The article deals with phyto-pharmacological investigative work done on herbals beneficial in liver and gall bladder ailments.

KEY WORDS: Medicinal Plants, Hepatoprotective, Hepatotoxic, Liver, Gall Bladder.

INTRODUCTION

The liver plays an astonishing array of vital functions in the maintenance, performance and regulating homeostasis of the body. Liver is considered to be one of the most vital organs that functions as a centre of metabolism for nutrients such as

carbohydrates, proteins and lipids and excretion of waste metabolites. Additionally, it is also handling the metabolism the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction [1] and excretion of drugs and other xenobiotics from the body thereby providing protection against foreign substances by detoxifying and eliminating them. The bile secreted by the liver has, among other things, plays an important role in digestion. Enhanced lipid per oxidation during metabolism of ethanol may result in development of hepatitis leading to cirrhosis. Since time immemorial, mankind has made the use of plants in the treatment of various ailments. The Indian Traditional Medicine like Ayurvedic, Siddha and Unani are predominantly based on the use of plant materials. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. The association of medical plants with other plants in their habitat also influences their medicinal values in some cases. One of the important and well-documented uses of plant-products is their use as hepatoprotective agents. Hence, there is an ever increasing need for safe hepatoprotective agent.

Silymarin is a potent hepatoprotective drug having established place in hepatology practice. Silymarin is a flavono-lignan mixture obtained from seeds of *Silybum marianum*. Silymarin is a mixture of silybin, isosilybin, silychristin and silydianin. Research on Indian medicinal herbs like *Picrorhiza kurroa* (Kutaki) and *Andrographis paniculata* (Kalmegh) has thrown light on hepatoptotective activity and it is more promising than silymarin.

TREATMENT OF LIVER DISEASE:

Each liver disease will have its own specific treatment regimen. For example, hepatitis A requires supportive care to maintain hydration while the body's immune system fights and resolves the infection. Patients with gallstones may require surgery to remove the gallbladder. Other diseases may need long-term medical care to control and minimize the consequences of their disease.

In patients with cirrhosis and end-stage liver disease, medications may be required to control the amount of protein absorbed in the diet. The liver affected by cirrhosis may not be able to metabolize the waste products, resulting in elevated blood ammonia levels and hepatic

encephalopathy. Low sodium diet and water pills (diuretics) may be required to minimize water retention.

In those with large amounts of ascites fluid, the excess fluid may have to be occasionally removed with a needle and syringe (paracentesis). Using local anesthetic, a needle is inserted through the abdominal wall and the fluid withdrawn. Operations may be required to treat portal hypertension and minimize the risk of bleeding. Liver is the final option for patients whose liver has failed.

HERBAL TREATMENT:

Medicinal herbs are significant source of hepatoprotective drugs. Mono and poly-herbal preparations have been used in various liver disorders. According to one estimate, more than 700 mono and poly-herbal preparations in the form of decoction, tincture, tablets and capsules from more than 100 plants are in clinical use. A drug having beneficial effect on the liver is known as hepatoprotective drug. On the other hand, drugs having toxic affect on the liver are better known as hepatotoxic drugs. Clinical research has also shown that herbals have genuine utility in the treatment of liver diseases. The article deals with investigative work done on herbals beneficial in liver and gall bladder ailments.

CLASSIFICATION:

These are generally classified into 3 categories without any strict delineation amongst them.

- Anti Hepatotoxic agents: These generally antagonize the effects of any hepatotoxins causing hepatitis or any liver disease.
- Hepatotropic agents: These generally support or promote the healing process of the liver. In practice these two activities cannot be easily distinguished from each other.
- Hepatoprotective agents: These generally prevent various types of liver affections prophilactically. In general any hepatoprotective agent can act as an anti hepatotoxic or hepatotropic agent but the vice versa is always not true.

HEPATOPROTECTIVE 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. Despite the significant popularity of several herbal medicines in general, and for liver diseases in particular, they are still

unacceptable treatment modalities for liver diseases. The limiting factors that contribute to this eventuality are:

(i) Lack of standardization of the herbal drugs.

(ii) Lack of identification of active ingredients(s)/principles(s).

(iii) Lack of randomized controlled clinical trials (RCTs).

(iv) Lack of toxicological evaluation.

The use of natural remedies for the treatment of liver diseases has a long history, starting with the Ayurvedic treatment, and extending to the Chinese, European and other systems of traditional medicines. The 21st century has seen a paradigm shift towards therapeutic evaluation of herbal products in liver disease models by carefully synergizing the strengths of the traditional systems of medicine with that of the modern concept of evidence-based medicinal evaluation, standardization and randomized placebo controlled clinical trials to support clinical efficacy [2].

A large number of plants and formulations have been claimed to have hepatoprotective activity. Nearly 160 phytoconstituents from 101 plants have been claimed by Pharmacopeia Foundation to possess liver protecting activity. In India, more than 87 plants are used in 33 patented and proprietary multi-ingredient plant formulations. In spite of the tremendous advances made, no significant and safe Hepatoprotective agents is available in modern therapeutics. Therefore, due importance has been given globally to develop plant-based hepatoprotective drugs, effective against a variety of liver disorders. The present review is aimed at compiling data based on reported works on promising phytochemical from medicinal plants that have been tested in hepatotoxicity models [3].

ABUTILON INDICUM

Hepatoprotective activity of *Abutilon indicum* on experimental liver damage in rats was studied by Porchezhian and Ansari [4] .They used carbon tetrachloride and paracetamol induced hepatotoxicity in rats. *A. indicum* exhibited significant hepatoprotective activity by reducing carbon tetrachloride and paracetamol induced change in bio-chemical parameters that was evident by enzymatic examination [5]. The plant extract may interfere with free-radical formation, which may conclude in hepatoprotective action. Acute toxicity studies revealed that the LD50 value is more than the dose of 4 g/kg body wt. They attributed the hepatoprotective activity to the inhibitory effects of drug on cytochrome P450 or/and promotion of its glucuronidation [6].

BORRERIA ARTICULARIS

The hepatoprotective activity of methanolic extract of *Borreria articularis* (*L.F) F.N. Willams:* (Rubiaceae) at doses of 250 mg/kg and 500 mg/kg were evaluated by carbon tetrachloride (CCl4) intoxication in rats[7]. The toxic group which received 25% CCl_4 in olive oil (1 ml/kg) per oral (p.o), alone exhibited significant increase in serum ALT, AST, ALP, and TB levels. It also exhibited significant ($P<0.001$) decrease in TP and ALB levels. The groups received pretreatment of *Borreria articularis* at a dose of 250 and 500 mg/kg b.w.p.o. had reduced the AST, ALT, ALP and TB levels and the effects were compared with standard drug (Silymarin100mg/kg b.w.p.o).The total protein (TP) and albumin (ALB) levels were significantly increased in the animals received pretreatment of the extract at the moderate and higher dose levels and the histo-pathological studies also supported the protective effect of the extract [8].

CITRUS MICROCARPA

The Philippine Department of Health stated that liver cancer is the third common forms of cancer for both males and females, hence the need for more hepatoprotective agents[9] . Silymarin, from milk thistle is the most well known hepatoprotective agent but due to availability and economic concerns with the use of milk thistle other sources were explored. Fruit peels constitute a bulk in Philippine wastes. If such wastes can be used as hepatoprotective agents, then wastes will be decreased and new sources of important products may be discovered.

This study was aimed to evaluate the hepatoprotective activity of *Citrus microcarpa* Bunge fruit peel extract relative to the commercially available Silymarin preparations. The chemical components of the fruit peels were analyzed to ascertain pharmacologic value. The study used an experimental research design using BFAD- Sprague Dawley rats as subjects. The hepatoprotective activity was evaluated based on changes in the liver morphology- gross examination and differences in serum liver enzyme levels- bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (AP) within and among the groups of rats. There was a significant decrease in ALT, AST and AP levels among rats administered with the fruit peel extract. Silymarin significantly decreased bilirubin levels. These suggest a comparable hepatoprotective activity between Silymarin and the fruit peel extract tested. Phytochemical analysis showed that the fruit peel extract

contained flavonoids, tannins, and glycosides. Quantitative analysis on the chemical components of the fruit peel extract is suggested to facilitate the study of its exact mechanism of action. Research on the protective ability of the fruit peel extract on other organ systems is recommended.

It is also suggested that other chemical liver toxicity inducers be used to observe the range of hepatoprotective activity of the fruit peel extract studied [10].

ANDROGRAPHIS PANICULATA

King of Bitters botanically known as *Andrographis paniculata* is an ancient Indian medicinal herb, which has been used for centuries in Asia for its effects on various bodily functions and ailments, ranging from degenerative diseases to the common cold. It is known as Kalmegh and is used as a bitter ingredient in the Indian indigenous system of medicine. The leaves contain andrographolide, most active component of *Andrographis paniculata* is very bitter in taste [11].

One the most common therapeutic potential of *Andrographis paniculata* is its liver protective property, which is well established experimentally. Alcoholic extract of the leaves of *Andrographis paniculata* was found to be effective in prevention of liver damage.
In another study administration of *Andrographis paniculata* exhibited liver protective effects by enhancing activity of antioxidant enzymes like superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase along with the level of glutathione and decreasing the activity of lipid peroxidase which leads to generation of free radicals damaging the liver cells. Thus by means of its synergistic effects *Andrographis paniculata* exerts its well-known hepatoprotective action [12].

CICHORIUM INTYBUS

Cichorium intybus commonly known as Chicory is an indigenous perennial herb well reputed ancient Indian medicine as a liver tonic. Accordingly it has been used as ayurvedic medicine for gall and liver disturbances. It forms an important component of several important liver preparations in India. In preclinical studies an alcoholic extract of the Cichorium intybus was found to be effective against chlorpromazine - induced hepatic damage in adult albino rats.

Extracts of *Cichorium intybus* were screened for their ability to protect the CCl_4 and paracetamol intoxicated liver in rats and were found to possess significant anti-hepatotoxic properties. Study done by using ethanol extract of *Cichorium intybus* in dose of 300 mg/kg showed significant increase in circulating leukocytes and relative weights of liver, as compared with alcohol alone which provides the evidence for liver protective effects of the herb[13] .

WEDELIA CALENDULACEA

Bhangra scientifically known as *Wedelia calendulacea*, belonging to Compositae family is a perennial herb, with light camphor-like odor. The plant is traditionally used as a tonic, for hepatic and spleen enlargement, and in skin diseases. Historical use of *Wedelia calendulacea* as liver tonic is scientifically confirmed.

Preclinical Studies demonstrate its protective action in paracetamol induced liver damage by increasing serum enzyme levels (lactate dehydrogenase, alanine and aspartate transaminase and alkaline phophatase). The alcoholic extract of whole plant *Wedelia calendulacea* exhibited protective activity against carbon tetrachloride-induced liver injury in vivo. The extract also increased the bile flow in rats suggesting a stimulation of liver secretory capacity. The minimum lethal dose was greater than 200 mg/kg p.o. in mice[14] .

BOERHAVIA DIFFUSA

The roots of *Boerhavia diffusa*, commonly known as 'Punarnava', are used by a large number of tribes in India for the treatment of various hepatic disorders and for internal inflammation. Anodectal data has also reported effectiveness of *Boerhavia diffusa* in cases of oedema and ascites resulting from early cirrhosis of the liver and chronic peritonitis. In scientific studies the chloroform and methanolic extracts of the roots and aerial parts of *Boerhavia diffusa* exhibited hepatoprotective activity against carbon tetrachloride[15].

A proprietary hepato-tonic herbal formulation containing *Boerhavia diffusa* as one of the major ingredient offered significant protection against decrease in haemoglobin percentage R.B.C. and W.B.C counts and the various liver microsomal enzymes[16] .

SALACIA RETICULATA

Salacia reticulata is a member of Hippocrateaceae family climbing shrub with blackish branches. The roots are traditionally used in treatment of gonorrhea, itches, swelling, diabetes and liver tonic. The Hepatoprotective effects extracts from the roots and stems of *Salacia reticulata* were examined using an oxidative stress-induced liver injury model[17] . Both extracts significantly suppressed the increase in glutamic oxaloacetic transaminase and glutamic pyruvic transaminase activities in carbon tetrachloride (CCl_4)-treated mice. These extracts also inhibited CCl_4-induced thiobarbituric acid-reactive substance formation, which indicates increased lipid peroxidation in the liver. These results suggest that the antioxidative activity is involved in the hepatoprotective activity of S. reticulate [18] .

PHYLLANTHUS AMARUS

Numerous medicinal plants and their formulations are used for liver disorder in Ethno medical practice and in traditional system in India. Indigenous plant *Phyllanthus amarus* was selected for clinical investigation of hepatoprotective activity. The ability of whole dried drug powder of *Phyllanthus amarus* (a traditionally used in the treatment of Jaundice) was tested for hepatoprotective activity on 107 patients who suffering from liver disease [19,31] . The powder of the herb was given thrice a day (morning, noon and night, 3 gm each time) orally with water for 30-45 days depending on the severity of the disease. The patients were evaluated for the changes in biochemical markers like SGPT, Billirubin and Haemoglobin on day zero, seven, fourteen, twenty one, twenty eight and forty two. There was significant decrease in SGPT, Billirubin and increase in hemoglobin [20,31] .

STACHYTARPHETA INDICA

The objective of the present study appraised the hepatoprotective activity of ethanolic extracts of S*tachytarpheta indica* (whole plant) on winstar rats. Liver damage was induced by intraperitonial administration of carbon tetrachloride (1ml/kg,b.w,p.o) for 7 days. The extent of damage was studied by assessing biochemical parameters. The ethanolic extracts of *Stachytarpheta indica* (300mg & 600mg/kg,b.w,p.o) were administered respectively to the animals treated with carbon tetrachloride and its effects on biochemical parameters were compared with standard drug solitarian (100mg/kg,b.w p.o). *Stachytarpheta indica* showed significant reduction of serum enzymes-AST, ALT, ALP, TP & Bilirubin (Aspartate

Transminase, Alanine Transminase, Alkaline Phosphatase, Total Protein & Total Billirubin) when compared to control rats[21]. The hepatoprotective effect of *Stachytarpheta indica* was comparable with the standard drug Silymarin. It was confirmed by histopathological study. The effect of extract 600mg/kg was almost equal to that of standard drug[22].

ECLIPTA ALBA

Eclipta alba Hassk. (Bhringaraja, Family: Compositae) is a perrenial shrub which grows widely in moist tropical countries.Different uses have been reported for this shrub. It is used as alterative, anthelmintic, expectorant, antipyretic, antiasthmatic, tonic, in hepatic and spleen enlargement, in skin diseases and as a substitute for Taraxacum (a popular liver tonic)[23]. Recently Chandra, have observed a significant anti-inflammatory activity of the powder in rats. It has been reported to be useful in liver ailments & has been shown to possess hepatoprotective activity against carbon- tetrachloride induced liver cell damage in animals . The effect of *Eclipta alba* (EA) extract was studied on paracetamol induced hepatic damage in Mice. Treatment with ethanol extract of *E. alba* was found to protect the the mice from hepato-toxic action of paracetamol as evidenced by significant reduction. in the elevated serum transaminase levels[24] .

FOENICULUM VULGARE

Fennel (*Foeniculum vulgare* Mill., family Umbelliferae) is an annual, biennial or perennial aromatic herb, depending on the variety, which has been known since antiquity in Europe and Asia Minor. The leaves, stalks and seeds (fruits) of the plant are edible. *Foeniculum vulgare* is an aromatic herb whose fruits are oblong, ellipsoid or cylindrical, straight or slightly curved and greenish or yellowish brown in colour[25] .Volatile components of fennel seed extracts by chromatographic analysis include transanethole, fenchone, methylchavicol, limonene, α- pinene, camphene, β-pinene, β-myrcene, α- phellandrene, 3-carene, camphor, and cisanethole [26]. Hepatoprotective activity of *Foeniculum vulgare* (fennel) essential oil was studied using a carbon tetrachloride-induced liver fibrosis model in rats[27]. The hepatotoxicity produced by chronic carbon tetrachloride administration was found to be inhibited by *Foeniculum vulgare* essential oil with evidence of decreased levels of serum aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and Billirubin[28].

TINISPORA CORDIFOLIA

Tinospora Cordifolia commonly known as Guduchi is one of the most valuable medicinal plant of ayurveda. According to Ayurvedic lexicons *Tinospora cordifolia* is referred to as "Amrita". The term "Amrita "is attributed to this drug in recognition to its ability to impart youthfulness, vitality and longevity to its patron. In modern medicine it is well known for its Hepatoprotective, Adaptogenic and Immunomodulatory activities[29]. Clinical studies in twenty patients of infective hepatitis showed that Guduchi plays an important role in relieving the symptoms as well as normalization of altered liver functions. The majority of cases i.e. 15 cases (75 %) were cured and 5 cases (25%) improved after treatment with *Tinospora cordifolia.*

Currently along with antibiotics and supportive intensive care management, immunotherapy with *Tinospora cordifolia* (Tc) is practiced in surgical units. This therapy has shown to boost host defenses and decrease the incidence of epticaemia, resulting in increased survival of patients. In experimental rats *Tinospora cordifolia* (100mg/kg/d for 5 weeks) was found to decrease the renal damage, improve the fibrinogen level, and reduce lead acetate induced endotoxaemia. *Tinospora cordifolia* was also found to decrease renal ischemia induced mortality to 36 percent. The prognosis following *Tinospora cordifolia* (Tc) appears to be due to protection against all the risk factors.

Kupffer cells are major determinants of outcome of liver injury. Their activity was therefore studied in a model of chronic liver disease. The effect of *Tinospora cordifolia*, with proven hepatoprotective activity, was evaluated on Kupffer cell function, using carbon clearance test as a parameter. Anti-hepatotoxic activity of *Tinospora cordifolia* was studied in albino rats intoxicated with CCl_4. Liver function was assessed based on morphological, biochemical (SGPT, SGOT, Serum alkaline phosphatase, Serum bilirubin) and functional (Pentobarbitone sleep time) tests. Efficacy of *Tinospora cordifolia* as a sole constituent in goats liver were studied. Results revealed clinical and hematobiochemical improvement at the later stages in *Tinospora cordifolia* treated goats, indicating that it has got hepatoprotective action[30] .

REFERENCES

1. Ward FM, Daly MJ. Hepatic Disease. In: Walker R. and Edwards C (eds.). Clinical Pharmacy and Therapeutics, New York; Churchill Livingstone: 1999, pp. 195-212.

2. Agarwal SS. Development of hepatoprotective formulations from plant sources. In: Gupta SK (ed.). Pharmacology and Therapeutics in the New Millennium, New Delhi; Narosa Publishing House: 2001, pp. 357-358.
3. Bone K, Mills S. Principles and Practices of Phytotheraphy. British Journal of Phytotheraphy, 2001; 12(2):107-13.
4. Porchezhian E, Ansari SH. Hepatoprotective activity of Abutilon indicum on experimental liver damage in rats. Phytomedicine international journal of phytotherapy and phytopharmacology, 2005; 12(1): 62–74.
5. Kirtikar KR., Basu BD. Indian Medicinal Plants, 2nd ed., Vol.1. India; Bishen Singh, Mahendra Pal Singh:1980, pp. 314–15.
6. Rajurkar R, Jain R, Matake N, Aswar P, Khadbadi SS. A Review on Some Important Medicinal Plants of Abutilon spp. Research J Pharm and Tech, 2009; 2(2): 415-16.
7. Pedro A, De Sa PN, Maria VS, Nadja CV, Zenaldoporfirio luiz CD. Antibacterial activity of *Borreria verticilata* roots. Fitoterepia, 2002; 73(1): 529-531.
8. Parameshwar H, Mohan GK, Kumar BR, Reddy YN. Hepatoprotective effect of the methanolic extract of whole plant of Borreria Articularis on Carbon Tetrachloride induced Hepatotoxicity in Albino Rats. Journal of Pharmaceutical Research and Health Care, 2001; 2(4): 285-292.
9. Jain A. A comparative study of ethanol extract of leaves of Tephrosia purpurea and the flavonoid isolated for hepatoprotective activity, Indian J Pharm Sci, 2006; 68(1): 740-743.
10. Chopra RN, Nayar SL, Chopra IC. Glossary of Indian Medicinal Plants, New-Delhi; CSIR: 1956. pp. 39-40.
11. Trivedi NP, Rawal UM. Hepatoprotective and antioxidant property of *Andrographis paniculata* (Nees) in BHC induced liver damage in mice. Indian J Exp Biol, 2001;39 (1): 41-46.
12. Shukla B, Visen PK, Patnaik GK and Dhawan BN. Cholretic effect of Andrographolide in rats and guinea pigs. Planta Med, 1992; 58(2):146-149.
13. Sultana S, Perwaiz S, Iqbal M, Athar M. Crude extracts of hepatoprotective plants, *Solanum nigrum* and *Cichorium intybus* inhibit free radical-mediated DNA damage. J Ethnopharmacol, 1995; 45(3):189-92.
14. Kokate CK, Purohit AP, Gokhakle SB. Analytical Pharmacognosy. 5th ed. India; Nirali prakashan; 1997. pp. 119-137.

15. Chandan BK, Sharma AK and Anand KK. *Boerhaavia diffusa*: a study of its hepatoprotective activity. *J Ethnopharmacol* 1991 Mar; 31(3):299-307.
16. Rawat AK, Mehrotra S, Tripathi SC and Shome U. Hepatoprotective activity of *Boerhaavia diffusa* L. roots- a popular ethno medicine. J Ethnopharmacol, 1997; 56(1) :61-6.
17. Bailey LH. Standard encyclopedia of Horticulture. vol. 2, New York; Mc Millan Co., 1928-29.
18. Kjaer A, Wagnieres M. 3,4,5-Trimethoxybenzylglucosinolate: A constituent of *Lepidium sordidum.* Phytochemistry ,1971; 10(1): 2195-2197.
19. RB, Raval JD, Gandhi TP, Chakravarthy BK. Traditional hepatoprotective drugs. Indian Drug, 1998; 25(6):224.
20. Rege N, Dahanukar S, Karandikar SM. Hepatoprotective activity of *Phyllanthus amarus.* Indian Drugs, 1984; 31(2): 569.
21. Otinmeyin OS, Vguru OM, Akanbi BE. Antidiarroheal effect of aqueous extract of *Momordica balsamnia* and *Stachytarpheta indica* in rats. J Natural products, 2008; 12(1) :36-45
22. Handa SS, Sharma A, Chakraborti KK. Natural products and plants as liver protecting drugs. Fitoterapia, 1986; 57(2) :307-345.
23. Chopra RN, Nayar SL, Chopra IC. Glossary of medicinal plants. New Delhi; CSIR Publication, 1966; pp. 104.
24. Khin M, Nyunt N, Maung T. The protective effects of *Eclipta alba* on carbon tetrachloride Induced Acute Liver Damage. Toxicol And Applied Pharmacol, 1978; 45 (1): 723-728.
25. Warrier PK, Nambiar VPK, Ramankutty C. Foeniculum vulgare. In: Indian Medical Plants. Volume 3. Chennai. Orient.1978.
26. Simándi BDA, Rónyani E, Yanxiang G, Veress T, Lemberkovics È, Then M, Sass-Kiss Á, Vámos- Falusi Z. Supercritical carbon dioxide extraction and fractionation of Fennel oil. J Agric Food Chem, 1999; 47(1): 1635-1640.
27. Hanefi Ö, Serdar U, Irfan B, Ismail U, Ender E, Abdurrahman Ö, Zübeyir HS. Hepatoprotective effect of Foeniculum vulgare essential oil: A carbon-tetrachloride induced liver fibrosis model in rats. J. Lab Anim Sci, 2004; 3(1): 168-172.
28. Khosla P, Gupta DD, Nagpal RK. Effect of Trigonella foenum graecum (Fenugreek) on serum lipids in normal and diabetic rats. International Journal of Pharmacology,1995; 27(1): 89–93.

29. Anonymous. Indian Herbal Pharmacopoeia Volume 1. Worli, Mumbai: Indian Drug Manufacturers Association; 1998.
30. Kapoor LD. CRC Handbook of Ayurvedic Medicinal Plants. Boca Raton; CRC Press:1990.
31. Patel JH, Patel JS, Patel KN, Seth AK, Patel KD. Clinical study of hepatoprotective drug Phyllanthus amarus. Research Journal of Pharmaceutical, Biological and Chemical Science, 2010; 1(2): 335-340.