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Journal of Advanced Scientific Research

J.Adv.Sci.Res, 2011, 2(2); 15-20
Review Article

ISSN: 0976-9595

POTENT HERBAL HEPATOPROTECTIVE DRUGS- A REVIEW

Akhil Bhardwaj[1*]
Pankaj Khatri[2]
M.L. Soni[1]
D.J. Ali [3]
[1]Department of Pharma-Biotechnology, Gyan Vihar School of Pharmacy
[2]Department of Pharmacognosy, Gyan Vihar School of Pharmacy
[3]Department of Biotyechnology, Gyan Vihar School of Sciences
Suresh Gyan Vihar University, Jagatpura, Jaipur-302025, Rajasthan, India
***Corresponding Author:**
akhiljs@gmail.com

ABSTRACT

Hepatic disease (Liver disease) is a term for a collection of conditions, diseases, and infections that affect the cells, tissues, structures, or functions of the liver. Liver has a wide range of functions, including detoxification, protein synthesis, and production of biochemical necessary for digestion and synthesis as well as breakdown of small and complex molecules, many of which are necessary for normal vital functions. There are no specific allopathic medicines uses as hepatoprotective, although different research works are going on some drug. Herbal drugs are more widely used than allopathic drugs as hepatoprotectives because of them are inexpensive, better cultural acceptability, better compatibility, with the human body and minimal side effects. In the current review, it had been tried to redefine the use of important herbal hepatoprotective drugs like *Andrographis paniculata*; *Swertia Chirata* etc. that consist of specific chemical constituents who have their specific hepatoprotective activity against hepatotoxicant like ethanol, drugs, chemicals and others. These herbal drugs have shown the ability to maintain the normal functional statues of the liver with or without fewer side effects. These are the reason that's why herbal hepatoprotectives are mostly preferred by medical practitioners, as well as over-the-counter.

Keywords: Hepatoprotective, Herbal, Phytoconstituents

INTRODUCTION

LIVER PHYSIOLOGY & HEPATIC DISEASE

The liver is the largest glandular organ in the body, and has more functions than any other human organ. A person's entire blood supply passes through the liver several times a day; The Liver has a pivotal role in human metabolism. Liver produces and secretes bile, it also produces prothrombin and fibrinogen, both blood clotting factors, and heparin, a muco-polysaccharide sulfuric acid ester that helps keeps blood from clotting within the circulatory system. The liver converts sugar into glycogen, Liver diseases have become one of the major causes of morbidity and mortality in man and animals all over globe and hepatotoxicity due to drugs appears to be the most common contributing factor[1].

Among the many diseases that can affect the liver the most common is 'viral hepatitis' (Inflammation of liver caused by viral infection). Hepatitis can be caused by drugs, viruses, bacteria, mushrooms, parasites like amoebas or giardiasis. About 20,000 deaths found every year due to liver disorders. The use of natural remedies for the treatment of liver diseases has a long history and medicinal plants and their derivatives are still used all over the world in one form or the other for this purpose. 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 contain active principles with curative properties against a variety of diseases[2]. Liver protective plants contain a variety of chemical constituents like phenols, coumarins, lignans, essential oil, monoterpenes, carotinoids, glycosides, flavonoids, organic acids, lipids, alkaloids and xanthenes[3]. Recent experience has shown that plant drugs are relatively non-toxic, safe and even free from serious side effects[4]. This review article has been presented to enumerate some indigenous plants that have hepatoprotective properties.

SYNTHETIC HEPATOPROTECTIVE DRUGS

There are no specific allopathic medicines used as hepatoprotective, although different research works are going on some drug like that *Rimonabant* chemically described as N–piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)–4–methyl-pyrazole–3–carboxamide, is selective endocannabinoid (CB1) receptor antagonist, inhibits the pharmacological effects of cannabinoids agonists *in vitro* and *vivo* and has hepatoprotective activity against hepatotoxicant like ethanol. It has seen that administration of rimonabant at 2.5mg/k, 5mg/kg and 10mg/kg dose level attenuated the increased level of the serum enzymes, produced by Ethanol and caused a subsequent recovery towards normalization almost like that of Silymarin treatment[5].

Steroids like corticosteroids are under the study for their hepatoprotective action[4]. Many other therapeutic interventions have been studied in alcoholic hepatitis, but have not been able to show convincing benefit, including trials of *anti-oxidants* (vitamin E, and combination anti-oxidants), *anti-fibrotics* (colchicine), *anti-thyroid drugs*, *promoters of hepatic regeneration* (insulin and glucagon), *anabolic steroids* (oxandrolone and testosterone), as well as *calcium channel blockers* (amlodipine), *polyunsaturated lecithin*, and a number of complementary and alternative medicines[4]. A number of other agents have been tested in patients including propylthiouracil to decrease the hyper-metabolic state induced by alcohol[6].

Herbal drugs are more widely used than allopathic drugs as hepatoprotectives because of them are inexpensive, better cultural acceptability, better compatibility, with the human body and minimal side effects. In other hand side effects, interactions, contra-interactions and toxicity of synthetic medicines vary wildly from mild to severe include insomnia, vomiting, fatigue, dry mouth, diarrhea, constipation, dizziness, suicidal thoughts, hostility, difficulty sitting still, depression, mania, seizures, coma, anemia, hair loss, high blood sugar, shoplifting, swelling, impotency, panic attacks, confusion, fainting and death[7].

POTENT HEPATOPROTECTIVE PLANT DRUGS

ANDROGRAPHIS PANICULATA

Andrographis paniculata commonly known as kalmegh, kirayat, and the great king of bitters, is obtained from dried leaves and tender shoots of plant *Andrographis paniculata* Nees, family *Acanthaceae* and found in tropical and subtropical Asia, south-east Asia, Sri Lanka and India (specifically in Maharashtra, Karnataka, Utter Pradesh, Tamil Nadu, and Assam etc)[8-9]. Leaves of *Andrographis paniculata* are dark in color, simple, opposite, lanceolate, glabrous, 2–12cm long, 1–3cm wide; acute apex, entire margin. Flower consists of small, linear 5-particle Calyx; tube narrows, about 6 mm long white corolla with violet markings. Two stamens, inserted in the throat and two celled superior ovary. 1–2 cm long, 2–5 mm wide, linear-oblong, compressed, erected capsule. Drugs have slight, characteristic odour and intensely bitter taste[10-11]. Microscopically drug have diacytic stomata at leaf's lower epidermis, glandular and non-glandular trichomes, fairly large cystoliths, columnar palisade cells, collenchymas in midrib beneath epidermis; spongy parenchyma cells; vascular bundles of lignified spiral, scalariform and reticulate xylem vessels in the upper part and lignified phloem in the lower part, small acicular calcium oxalate crystals, a layer of wavy-walled lower epidermis cells, dense collenchyma at the corners of stems, a layer of thick-walled endodermis cells and parenchyma contains chloroplastid.

The major phyto-constituents of *Andrographis paniculata* are diterpene lactones (free and in glycosidic forms) including andrographolide, deoxyandrographolide, 11, 12-didehydro-14-deoxyandrographolide, neoandrographolide, andrographiside, deoxyandrographiside and andropanoside[8-11]. There structures are following as in fig.1:-

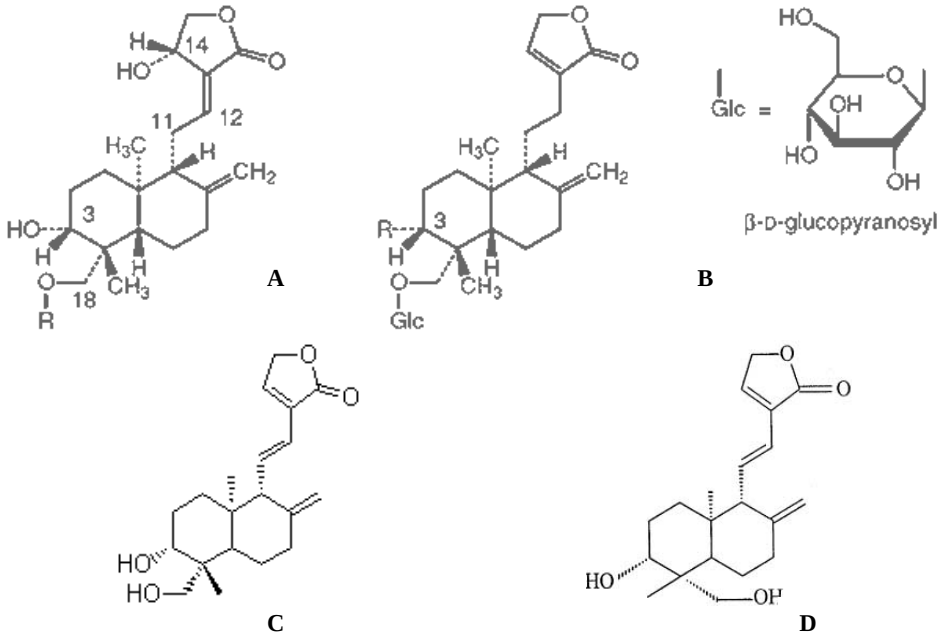


Figure1: Structures of "A"- Andrographolide R=H, Andrographiside R = Glc; "B"- Neoandrographolide R = H, Andropanoside R = OH; "C"- Dehydroandrographolide; and "D"- Deoxyandrographolide.

Andrographis paniculata should have foreign organic matter not more than 2%; Acid-insoluble ash not more than 2%; Water-soluble extractive not less than 18%; Alcohol-soluble extractive not less than 13% using 85% ethanol; Loss on drying not more than 10%.[9]

Studies proved that *Andrographis paniculata* (kalmegh) Antihepatotoxic activity of the *Andrographis paniculata* (acanthaceae) methanolic extract (equivalent to 100 mg/kg of andrographolide) and 761.33 mg/kg ip, of the andrographolide-free methanolic extract (equivalent to 861.33 mg/kg of the methanolic extract) of the plant, using CCl_4-intoxicated rats. Biochemical parameters like serum transaminases, SGOT and SGPT, serum alkaline phosphatase, serum bilirubin and hepatic triglycerides were estimated to assess the liver function. The results suggest that andrographolide is the major active antihepatotoxic principle present in *A. paniculata*[12].

Other species of *Andrographis* i.e *Andrographis lineata nees* had also proved hepatoprotective effect of *Andrographis lineata* (Acanthaceae) extracts in CCl_4- induced liver injury in rats. Male Wistar rats with chronic liver damage, induced by subcutaneous injection of 50% v/v CCl_4 in liquid paraffin at a dose of 3 mL/kg on alternate days for a period of 4 weeks, were treated with methanol and aqueous extracts of A. lineata orally at a dose of 845 mg/kg/day. The biochemical parameters such as serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, serum bilirubin and alkaline phosphatase were estimated to assess the liver function. Histopathological examinations of liver tissue corroborated well with the biochemical changes. The activities of extracts were comparable to a standard drug[13].

Hepatoprotective Action of Andrographis paniculata

Andrographolide, the major antihepatotoxic component of the plant, exerted a pronounced protective effect in rats against hepatotoxicity induced by CCl4, Dgalactosamine, paracetamol and ethanol. Andrographolide inhibited the CCl4-induced increase in the activity of serum glutamate oxaloacetate transaminase, serum glutamate pyruvate transaminase, alkaline phosphatase, bilirubin and hepatic triglycerides. Oxidative damage through free radical generation involved in the hepatotoxic effect of carbon tetrachloride (CCl_4) and paracetamol (PC). An anti-oxidant property of Andrographolide is claimed to be one of the mechanisms of hepatoprotective effect. Adjuvant to hepatoprotective action drug is commonly have Antibacterial, Anti-inflammatory, Immunostimulatory, Antidiarrhoeal, Anti-human immunodeficiency virus (HIV), Antipyretic, Antimalarial &Antivenom activity, and used in urinary infections[9-12].

Pharmacokinetics

When orally consumed, androgreapholide appears to accumulate in organs throughout the viscera. Pharmacokinetic studies showed that androgreapholide is quickly absorbed and extensively metabolized in rat and human. 90% is eliminated within 48 hr. These metabolites are mainly identified as sulfonic acid aducts and sulfate compound as well as glucuronic conjugation. Ten metabolites of androgreapholide as sulfonate, sulfate ester compounds and androgreapholide analogues were isolated from rat urine, feces. While those metabolites are isolated from human urine were as sulfate, cysteine S conjugate and glucuronide conjugates[10-11].

Adverse Reactions

Large oral doses may cause gastric discomfort, vomiting and loss of appetite due to the bitter taste of andrographolide. Anaphylactic reactions may occur if the crude drug extract is injected so crude extracts of Herba Andrographidis should not be injected[9].

Drug Interactions

Extracts of Herba Andrographidis may have a synergistic effect with isoniazid[9] and also have interaction with anticoagulants, antidiabetics, anthypertensive, and antiplatelet .

Contraindications

Herba Andrographidis should not be used during pregnancy or lactation and In vivo studies in mice and rabbits suggest that Herbal Andrographidis may have abortifacient activity. Since potential antagonism exists between Herba Andrographidis and endogenous progesterone, Herba Andrographidis should not be used during pregnancy. Herba Andrographidis is contraindicated in cases of known allergy to plants of the *Acanthaceae* family[9].

SWERTIA CHIRATA

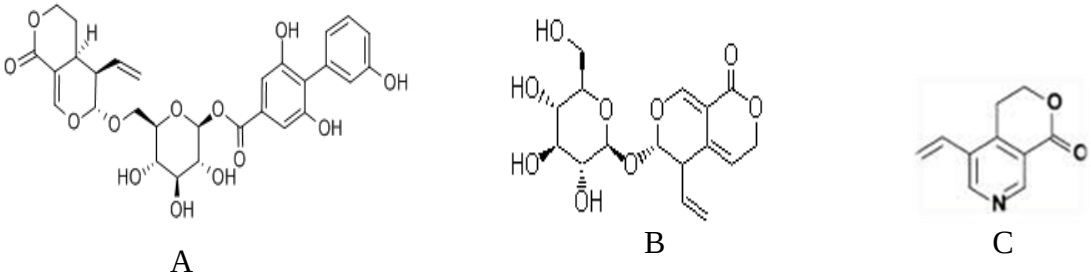
Swertia chirata commonly known as clearing nut tree, bitter stick, Indian chirette, dowa I pechish, Indian gentian is consist of the entire herb of *Swertia chirata* Buch Ham, belonging to family *Gentianceae*, found in India (Kashmir, Meghalaya, Madhya Pradesh, and Khasi hills), Nepal and Bhutan[10, 25].

Extremely bitter and odourless drug have yellowish tinge leaves, flowers and fruits, yellowish-brown to purple stems; ovate or lanceolate leafs with entire margin; superior, bicarpellary unilocular fruits with numerous reticulated ovoid seeds; and about 5-10 cm long, brown, twisted, tapering root with root-lets[8, 13].

Transverse section of root shows, 2-4 layers of cork, thick-walled parenchymataous secondary cortex cells with mucilage, minute acicular crystals (also in present phloem region), and resin (as dark brown mass); secondary phloem composed of thin-walled strands of sieve tubes, companion cells and phloem parenchyma; lignified and thick-walled scalariform, simple

and bordered pitted secondary xylem vessels, tracheids parenchyma and xylem fibers. Transverse section of Stem shows, single layered epidermis; parenchymatous cortical cells with Mucilage, minute acicular crystals, resin (as dark brown mass), and oil droplets; endodermis; single thin walled pericycle cells layer; rounded and isodiametric pith cells with prominent intercellular spaces. Transverse section of leafs shows single epidermis layer covered with a thick, striated cuticle, more strongly developed on the upper surface than the lower; anisocytic stomata; single layered palisade tissue, spongy messophyll cells with minute acicular crystal and Mucilage[13].

Swertia chirata contains bitter yellow acid known as ophelic acid, two bitter glycosides chiratin (not a pure substance) and amarogentin (phenol carbonic acid ester of sweroside, a substance related to gentiopicrin), two alkaloids gentianine and gentiocrucine and also contains yellow crystalline substance used in dyeing[8, 13]. There structures are following as in fig.3.



A B C

Figure 3: Structure of "A" Amarogentin, "B" Gentiopicrin "C" Gentianine.

Drug should have[13] foreign organic matter not more than 2%, total ash not more than 6%, acid-insoluble ash not more than 1%, water-soluble extractive not less than 10%, alcohol(60%)-soluble extractive not less than 10%.

Hepatoprotective Action of Swertia Chirata

Due to effect of hepatotoxicant (like ethanol, drugs, chemicals and others) serum aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), and alkaline phosphatase (ALP) activities and bilirubin level are increased, but liver glycogen and serum cholesterol levels are decreased. Histologically it produced hepatocytic necrosis especially in the centrilobular region. Simultaneous treatments with *Swertia chirata* caused improvement at both biochemical and histopathological parameters. Drug also possesses digestive, hepatic (conditions pertaining to the liver), tonic, astringent and appetizer properties and used in cough, dropsy and skin diseases[13-14].

Swertia Chirata (Chirayata) Simultaneous treatments with *S. Chirata* (Gentianaceae). (in different doses, viz. 20, 50, and 100 mg/kg body wt daily) and (CCl4) caused improvement at both biochemical and histopathological parameters compared to that of (CCl4) treatment alone but it was most effective when S. chirata was administered in a moderate dose (50 mg/kg body wt)[15].

Pharmacokinetics

The pharmacokinetics studies are going on in process but presently there are no significant Pharmacokinetics study has been reported.

Adverse Reactions/Drug Interactions/Contraindications

In case of *Swertia chirata*, till now experimentally there is no adverse effect, drug interaction, contraindication, or toxicity has been observed. *Swertia chirata* should be avoided by people with gastric or duodenal ulcers. This herb is considered safe when taken as prescribed. Do not medicate yourself with this herb; only use it under the supervision of a qualified practitioner[16].

OTHER POTENT HEPATOPROTECTIVE PLANT DRUGS

Azadirachta indica (Neem)

Effect of *A. indica* leaf *(meliaceae)* extract on serum enzyme levels (glutamate oxaloacetate transaminase, glutamate pyruvate transaminase, acid phosphatase and alkaline phosphatase) elevated by paracetamol in rats was studied with a view to observe any possible hepatoprotective effect of this plant. It is stipulated that the extract treated group was protected from hepatic cell damage caused by paracetamol induction. The findings were further confirmed by histopathological study of liver.The antihepatotoxic action of picroliv seems likely due to an alteration in the biotransformation of the toxic substances resulting in decreased formation of reactive metabolites[17].

Careya arborea

The methanol extract of *Careya arborea bark*, (myrtaceae) was tested for antioxidant and hepatoprotective activity in Ehrlich ascites carcinoma (EAC) tumor-bearing mice. Tumor control animals inoculated with EAC showed a significant alteration in the levels of antioxidant and hepatoprotective parameters. The extract treatment at 50, 100 and 200 mg/kg body weight doses given orally caused a significant reversal of these biochemical changes towards the normal in serum. Liver and kidney when compared to tumor control animals indicating the potent antioxidant and hepatoprotective nature of the standardized extract[18].

Cassia fistula (Amaltas)

Hepatoprotective activity of the n-heptane extract of *Cassia fistula* (Fabaceae) leaves was investigated by inducing hepatotoxicity with paracetamol in rats. The extract at a dose of 400 mg/kg body wt. exhibited orally, significant protective effect by lowering the serum levels of transaminases (SGOT and SGPT), bilirubin and alkaline phosphatase (ALP). The effects produced were comparable to that of a standard hepatoprotective agent[19].

Eclipta Alba (Bhringaraj)

The hepatoprotective effect of the ethanol/water (1:1) extract of *Eclipta Alba* (Asteraceae) was studied at subcellular levels in rats against (CCl4) -induced hepatotoxicity. The loss of hepatic lysomal acid phosphatase and alkaline phosphatase by (CCl4) was significantly restored by *Eclipta Alba*. The study shows that hepatoprotective activity of *Eclipta Alba* is by regulating the levels of hepatic microsomal drug metabolising enzymes[20].

Fumaria indica (Hauskn)

Fumaria indica (Fumariceae) were studied for their hepatoprotective activity against carbontetrachloride, paracetamol and rifampicin-induced heptatotoxicites in albino rats. The petroleum ether extract against carbonetrachloride, total aqueous extract against paracetamol and methanolic extract against rifampicin-induced hepatotoxicities showed similar reductions in the elevated levels of some of the serum biochemical parameters in a manner similar that of silymarin indicating its potential as a hepatoprotective agent[21].

Morinda citrifolia L. (Noni)

The hepatoprotective effects of Noni juice (TNJ) (Rubiaceae) against CCl_4-induced chronic liver damage in female Sprague Dawley (SD) rats. Histopathological examination revealed that liver sections from the TNJ + CCl_4 appeared similar to controls, whereas typical hepatic steatosis was observed in the placebo + CCl_4 group. Serum alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine transaminase (ALT), total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) levels were increased in the placebo group compared with the TNJ group. In contrast, high-density lipoprotein (HDL) was increased in the TNJ group and decreased in the placebo group. Thus, TNJ juice appears to protect the liver from chronic exogenous CCl_4 exposures[22].

***Phyllanthus amarus (Bhuiamala*)**

Ethanolic extract of *Phyllanthus amarus* (euphorbiaceae), at (0.3g kg (-1) BW 0.2 ml (-1) day (-1) was given to all groups except control groups (gp. I and gp. V), after 30 min of aflatoxin administration. The entire study was carried out for 3 months and animals were sacrificed after an interval of 30 days till the completion of study. *Phyllanthus amarus* extract was found to show hepatoprotective effect by lowering down the content of thiobarbituric acid reactive substances (TBARS) and enhancing the reduced glutathione level and the activities of antioxidant enzymes, glutathione peroxidase (GPx), glutathione-S transferase (GST), superoxide dismutase (SOD) and catalase (CAT) [23].

Picrorhiza kurroa (Kutki)

Administration of picroliv, a standardized fraction of alcoholic extent of *Picrorhiza kurroa* (Scrophulariaceae) (3-12 mg/kg/day for two weeks) simultaneously with P. berghei infection showed significant protection against hepatic damage in Mastomys natalensis. The increased levels of serum glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transaminase (GPT), alkaline phosphatase, lipoprotein-X (LP-X) and bilirubin in the infected animals were marked reduced by different doses of picroliv. In the liver, picroliv decreased the levels of lipid peroxides and hydroperoxides and facilitated the recovery of superoxide dismutase and glycogen[24].

Solanum nigrum (Makoi) and ***Cichorium intybus (Kasni)***

The presence of plant extracts of *Solanum nigrum* (solanaceae) and *Cichorium intybus* (Asteraceae) in the reaction mixture containing calf thymus DNA and free radical generating system protect DNA against oxidative damage to its deoxyribose sugar moiety. The effect was dependent on the concentration of plant extracts. However, the effect of Cichorium intybus

was much pronounced as compared to the effect of *Solanum nigrum*. These studies suggest that the observed hepatoprotective effect of these crude plant extracts may be due to their ability to suppress the oxidative degradation of DNA in the tissue debris[25].

Wedelia calendulacea L (Bhanra)

Hepatoprotective activity of the ethanolic-leaf extract of *W.calendulacea* (Asteraceae) (EEWC) was studied by estimating serum enzyme activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), protein and bilirubin. 4 The treatment with EEWC showed a dose-dependent reduction of CCl_4 induced elevated serum levels of enzyme activities with parallel increase in total protein and bilirubin, indicating the extract could preserve the normal functional status of the liver[26].

DISCUSSION

From the different studies, it can say that these herbal drugs are proved to be one of the best herbal medications for liver disease. These herbal drugs including *Andrographis paniculata* and *Swertia chirata* consist of specific chemical constituents who have their specific hepatoprotective activity against hepatotoxicant like ethanol, drugs, chemicals and others. These herbal drugs have shown the ability to maintain the normal functional statues of the liver with or without fewer side effects. These are the reason that's why herbal hepatoprotectives are mostly preferred by medical practitioners.

FUTURE PROSPECTS

It has been seen that herbal hepatoprotective drugs have less side effect or interaction as compare to synthetic medicine but in other hand scientific evidence from tests done to evaluate the safety and effectiveness of traditional hepatoprotective medicine products and practices is limited and further study of products and practices is needed. Pharmacokinetic and toxicity studies have not disclosed any issues that could limit the therapeutic use of these drugs. Also the study is required to identify glycosides, flavonoids, triterpenes and phenolic compounds as classes of compounds with hepatoprotective activity. Further studies including clinical trials need to be carried out to ascertain the safety of these compounds as a good alternative to conventional drugs in the treatment of liver diseases.

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