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A COMPREHENSIVE REVIEW ON THE HEPATOPROTECTIVE EFFICACY OF MEDICINAL PLANTS

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ABSTRACT
Plants have been found to possess decent medicinal properties from the time immemorial. There are thousands of plants with antidiabetic, nephroprotective, antioxidant, anticancerous, antiarthritic and antiinflamatory effects. In the present review, an attempt has been made to compile the data related to the importance of the plants with special emphasis on their hepatoprotective nature. This paper may be very much helpful to the people working in the fields of health, therapeutics, pharmacognosy and pharmacology.

KEYWORDS: Medicinal plants, antioxidants, liver marker enzymes, hepatoprotection, pharmacology.

1. INTRODUCTION
Liver, the largest internal organ found in the human body is closely associated with the small intestine and process the nutrient-enriched venous blood that leaves the digestive tract. It has been found to perform over 500 metabolic functions, which finally leads to the synthesis of products that are released into the blood stream (e.g. glucose derived from glycogenesis, plasma proteins, clotting factors and urea), or that are excreted to the intestinal tract (bile). Also, several products like glycogen, fat and fat soluble vitamins are stored in liver parenchyma.

Because of the immense importance of the liver in the body, liver disorders severely and negatively affect the quality of life and life expectations. Most of the liver ailments are caused by the exposure to toxic substances, metabolic disorders, viruses and genetic abnormalities. Even though, the advancement in the modern medicine is tremendous, there is no effective drug available that stimulates liver function, offer protection to the liver from damage or help to regenerate hepatic cells (Chatterjee, 2000).

Numerous medicinal plants and their formulations are used for liver disorders in ethnomedical practices and in traditional system of medicine in India. Most of the herbal drugs speed up the natural healing process of liver. So, the search for effective hepatoprotective drugs continues.

The present review is an effort to pile up the data regarding the hepatoprotective potential of herbal extracts in combating the liver ailments using scientific systems which researchers have elucidated from time to time.

2. METHODOLOGY
In present review, the literature search was done up to February, 2017, using Pubmed, Elsevier-Science direct, SpringerLink (Springer/Kluwer), Wiley Interscience (Wiley) and Google Scholar search engine. The following keywords viz. plants, medicinal plants, plant formulations, hepatoprotective potential and liver disorders were used in searching process.

3. Hepatoprotective potential of various medicinal plant extracts

3.1. *Curculigo orchioides*
Venukumar and Latha (2002) explored the protective nature of methanolic extract of *Curculigo orchioides* rhizomes in rats against carbon tetrachloride toxicity. All the marker enzymes, *viz.*, AST, ALT and ALP registered increased levels in CCl_4-treated rats as compared to control group. However, in *Curculigo orchioides* rhizome extract group, the levels of these enzymes were found to retrieve towards normal.

3.2. *Sarcostemma brevistigma*
A significant diminution was noticed in SGPT, SGOT, ALP and total bilirubin levels in the groups of rats treated with silymarin + CCl_4 and ethyl acetate extract of *Sarcostemma brevistigma* bark + CCl_4 as compared to

that of only CCl_4 group. The levels of these parameters were almost restored to the normal. The investigators further observed that the dimension of the liver was enlarged in CCl_4-treated rats but it was regular in drug-treated groups. A significant fall in liver weight authenticated the above findings (Neoliya *et al.*, 2003).

3.3. *Epaltes divaricata*

Hewawasam *et al.* (2004) evaluated the antihepatotoxic efficacy of aqueous extract of *Epaltes divaricata* whole plant in mice exposed to CCl_4. They substantiated the protection by analyzing liver markers like AST, ALT and ALP in different groups of experimental mice. The authors noticed that the extract was sufficient enough to bring the elevated levels of liver markers towards the normal.

3.4. *Solanum trilobatum*

Shahjahan *et al.* (2004) observed that the levels of indicator enzymes of liver toxicity such as alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) were elevated significantly in the group of rats intoxicated with CCl_4. However, the alcoholic extract of whole plant of *Solanum trilobatum* brought the significant decrease in the levels of all these enzymes.

4.5. Ficus carica

Krishna *et al.* (2007) explored the protective effect of methanolic leaf extract of *Ficus carica* in rats exposed to carbon tetrachloride. The extract at an oral dose of 500 mg/kg displayed a significant protective effect by reducing the serum levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), total serum bilirubin and malondialdehyde equivalent in rats inebriated with CCl_4.

3.6. Asparagus racemosus (root), *Boerhaavia diffusa* (whole plant), *Glycyrrhiza glabra* (root), *Hemidesmus indicus* (root), *Phyllanthus amarus* (whole plant), *Phyllanthus emblica* (fruit), *Picrorhiza scrophulariiflora* (root), *Ricinus communis* (fruit) and *Tinospora cordifolia (stem)*.

Lal *et al.* (2007) assessed the efficacy of a herbal mixture of nine plants viz *Asparagus racemosus* (root), *Boerhaavia diffusa* (whole plant), *Glycyrrhiza glabra* (root), *Hemidesmus indicus* (root), *Phyllanthus amarus* (whole plant), *Phyllanthus emblica* (fruit), *Picrorhiza scrophulariiflora* (root), *Ricinus communis* (fruit) and *Tinospora cordifolia (stem)* in the form of tablets against CCl_4 induced hepatopathy in Swiss albino mice. They used a known hepatoprotective polyherbal drug as standard for comparison of their results. They observed the significant reduction in the levels of aspartate and alanine transaminases of liver injury in the herbal mixture treated groups, which was in line to the reduction initiated by Liv 52.

3.7. Urtica urens

Sen *et al.* (2007) reported the protective action of hexane extract of seeds of *Urtica urens* against the hepatotoxic effect of CCl_4 in rats. It was found that application of *Urtica urens* rendered the CCl_4 dependent elevated lipid peroxidation and serum, ALT and AST activities towards lower levels. Additionally, *Urtica urens* sheltered the ill effect of CCl_4 on CYP2E1 catalyzed aniline 4-hydroxylase activities.

3.8. Lepedium sativum

Abuelgasim *et al.* (2008) unfolded the defending power of chloroform seed extract of *Lepedium sativum* in rats inebriated with CCl_4. The authors assessed various biochemical parameters in their study like AST, ALP, ALT and bilirubin. They found that the extract offered the good protective effect by decreasing the levels of AST, ALP, ALT and bilirubin in carbon tetrachloride exposed group.

3.9. Trianthema decandra

Balamurugan and Muthusamy (2008) detected the curative potential of ethanolic root extract of *Trianthema decandra* in rats subjected to CCl_4 toxicity. They observed that the use of extract at different doses restored the levels of serum markers like AST, ALT, ALP and total bilirubin.

3.10. Pisonia aculeate

Palanivel *et al.* (2008) experimented the hepatoprotective effect of ethanolic leaf extract of *Pisonia aculeate* in rats exposed to CCl_4. They did the preliminary phytochemical screening of the extract and also determined the acute oral toxicity of *Pisonia aculeate* in rats. They also analysed the various biochemical parameters like AST, ALP, ALT, total bilirubin and total protein. The results led them to the conclusion that leaf extract of *Pisonia aculeate* is very much beneficial in treating the liver ailments.

3.11. Annona squamosa

Saleem *et al.* (2008) determined the protective effect of ethanol extract of *Annona squamosa* leaves in rats using isoniazid and rifampicin as toxicants for 21 days. The degree of protection was noticed by analyzing the biochemical parameters like ALP, AST and ALT in the groups of rats treated with isoniazid, rifampicin and ethanol extract of *Annona squamosa* and compared the results with that of only isoniazid and rifampicin exposed group. The extent of protection of the extract was compared with group of animals treated with standard drug Silymarin and combination of isoniazid rifampicin. It was concluded that ethanolic leaf extract of *Annona squamosa* is having good efficacy in curing the liver toxicity caused by carbon tetrachloride intoxication.

3.12. Rheum emodi

The aqueous and ethanolic extracts of root of *Rheum emodi* wall were compared for their hepatocurative property against CCl_4 induced toxicity in rats. The

defending effect was reviewed by quantifying serum alanine and aspartate transaminases (ALT and AST) and alkaline phosphatase (ALP) levels in different groups of experimental rats. The results showed the positive response in treating the liver damage caused by CCl_4 (Tahir *et al.*, 2008).

3.13. Artanena sesamoides

Selvan *et al.* (2008) reported the antioxidant potential of medicinal herb *Artanena sesamoides* aerial parts, in rats, using methanol as the solvent. The experiment was carried for 14 days, the analysis of the biochemical parameters e.g. serum glutamic oxaloacetic transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT) and alkaline phosphatase (ALP) in the Streptozotocin (STZ) infected group showed elevated levels indicating the hepatic damage along with decreased total protein level. However, the retrieval of the said biomarkers towards the normal levels by the methanol extract of *Artanema sesamoides* 200 and 400 mg/kg body weight indicates its efficiency in combating the liver damage.

3.14. Vitex trifolia

The CCl_4 elevated levels of ALT, AST, ALP and total bilirubin were put on a normal footing by the ethanolic extract of flowers of *Vitex trifolia* in rats. This hepatoprotective activity of the said extract was compared with the standard drug silymarin (Anandan *et al.*, 2009).

3.15. Cardiospermim helicacabum

Ara *et al.* (2009) demonstrated the hepatoprotective effect of various extracts of *Cardiospermim helicacabum* stem in rats exposed to CCl_4. They checked the presence of various phytochemicals in different extracts of *Cardiospermim helicacabum* stem by using standard procedures. The clinical conditions of the rats were assessed by using various biochemical parameters like protein, serum bilirubin, SGOT, SGPT and ALP. It was found that the *Cardiospermim helicacabum* extract normalized the levels of above liver markers.

3.16. Cochlospermum tinctorium

Etuk *et al.* (2009) validated the modulatory effect of aqueous root extract of *Cochlospermum tinctorium* in rats intoxicated with CCl_4. The investigators checked the presence of alkaloids, tannins, cardiac glycosides, saponins, flavonoids, triterpenes, cyanogenic glycosides, volatile oils, steroids and anthraquinones in the extract. They further noticed that CCl_4 intoxication caused the significant elevation in the levels of AST, ALT and ALP in rats. However, when *Cochlospermum tinctorium* extract was supplied to the rats inebriated with CCl_4, a significant reduction in the elevated levels of AST, ALT and ALP was noticed in comparison to that of only CCl_4 treated group of rats.

3.17. Acorus calamus

Palani *et al.* (2009) reported the hepatoprotective property of ethanol extract of medicinal herb *Acorus calamus* in rats treated with acetaminophen at a dose of 750 mg/kg body weight. The two doses of the extract of aerial parts at 250 mg/kg and 500 mg/kg body weight in rats treated with acetaminophen showed the protection as indicated by the decreased levels of SGOT, SGPT and ALP but higher level of total protein as compared to that of the only acetaminophen treated rats. The results were compared with the group of rats treated with standard drug Silymarin and were found to be satisfactory.

3.18. Mimosa pudica

Methanolic extract of *Mimosa pudica* leaves confirmed the significant hepatoprotective effect by decreasing the serum levels of various biochemical parameters such as serum glutamic oxaloacetate transaminase (SGOT), serum glutamic pyruvate transaminase (SGPT), alkaline phosphatase (ALP), total bilirubin (TBL), total cholesterol (CHL) and by increasing the levels of total protein (TP) and albumin (ALB) in carbon tetrachloride induced toxicity in rats (Rajendran *et al.*, 2009).

3.19. Capparis sepiaria

Satyanarayana *et al.* (2009) evaluated the antihepatotoxic effect of the alcoholic extract of *Capparis sepiaria* stem in rats exposed to CCl_4. They found that the extract produced significant reduction in the levels of aspartate transaminase (AST), alanine transaminase (ALT), total bilirubin (TB) and rise in total protein level when compared against the only CCl_4 inebriated group.

3.20. Colocasia antiquorum

Tuse *et al.* (2009) analysed the antihepatotoxic effect of *Colocasia antiquorum* in rats exposed to CCl_4 and paracetamol. They studied the behavioral changes and the lethality in the rats supplied with ethanol extract of *Colocasia antiquorum* (EECA) corms. In addition to that, they checked the levels of biochemical parameters like SGOT and SGPT in the rats supplied with EECA and also in the rats supplied with ethanolic extract of *Colocasia antiquorum* but intoxicated with paracetamol. However, the level of these parameters were restored to near normal levels in the later case.

3.21. Flacourtia indica

Animals were pretreated with the aqueous extract of *Flacourtia indica* leaves (250 and 500 mg/kg body weight) for one week and then confronted with CCl_4 (1.5 ml/kg bw) in olive oil (1:1, v/v) on 7^{th} day. Serum marker enzymes (ALP, AST, ALT, total protein and total bilirubin were estimated in all the study groups. Alteration in the levels of biochemical markers of hepatic damage like AST, ALT, ALP, total protein and total bilirubin were tested in both CCl_4 treated and extract treated groups. The CCl_4 intoxication elevated the levels of AST, ALT, ALP and total bilirubin but decreased the level of total protein. Treatment of aqueous extract of *Flacourtia indica* leaves (250 and 500 mg/kg) exhibited a significant protective effect by normalizing the serum levels of AST, ALT, ALP, total protein and total bilirubin (Gnanaprakash *et al.*, 2010).

3.22. Cassia fistula

Jehangir *et al.* (2010) reported the antihepatotoxic effect of *Cassia fistula* leaves in rats against isoniazid and rifampicin induced toxicity. They noticed the alterations in the levels of various biochemical parameters like AST, ALT, ALP and total bilirubin in different groups of rats. However, the groups supplied with the extract showed the satisfactory results.

3.23. Coccinia indica

Kumar *et al.* (2010) studied the hepatoprotective effect of diethyl ether extract of *Coccinia indica* leaves. Preliminary phytochemical analysis of the extract was done to detect if the extract is having carbohydrates, glycosides, alkaloids, tannins and flavonoids. The degree of hepatoprotection against CCl_4 was confirmed by analyzing the alterations in serum marker enzymes viz. SGOT and SGPT in different groups of rats.

3.24. Cocculus hirsutus

Noorani *et al.* (2010) induced the hepatotoxicity in rats by daily dose of ethanol up to 30 days as manifested by statistically significant increased levels of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and bilirubin. Pretreatment of rats with the methanolic extract of *Cocculus hirsutus* (whole plant) at different doses prior to ethanol dosing statistically decreased the serum liver enzyme activities. The activity of the extract was analogous to the standard drug silymarin.

3.25. Dillenia indica

Reddy *et al.* (2010) found that the levels of AST, ALT, ALP and bilirubin were significantly increased but protein content was significantly decreased in rats subjected to CCl_4 intoxication when compared with control group. However, treating the animals with hexane extract of *Dillenia indica* seeds at two different doses (250 and 500 mg/kg.b.wt) in CCl_4 treated rats showed drop off in the activities of serum enzymes and bilirubin and increased the level of protein when compared to the group of rats exposed to CCl_4 alone.

3.26. Tephrosia purpurea

Sangeetha and Krishnakumari (2010) evaluated the protective role of ethanolic extract of the root of *Tephrosia purpurea* in rats intoxicated with CCl_4. They analysed various biochemical parameters like AST, ALT, ALP, ACP (acid phosphatase) and total protein in their study. The level of these parameters were reinstated to normal with the root extract of *Tephrosia purpurea.*

3.27. Launaea intybacea

Takate *et al.* (2010) explored the protective effect of *Launaea intybacea* aerial parts against CCl_4 induced liver injury in rats. Silymarin was given as the reference standard. The hepatoprotective nature of the said plant was estimated by analyzing bilirubin, SGOT, SGPT and ALP levels in serum. They noticed the reasonable protection against CCl_4 toxicity in the rats supplied with the aqueous extract of *Launaea intybacea* aerial parts.

3.28. Berberis asiatica

Tiwari and Khosa (2010) substantiated the hepatoprotective effect of methanolic and aqueous extracts of *Berberis asiatica* aerial parts in rats subjected to CCl_4 toxicity. The investigators screened pet ether, methanolic and aqueous extracts for the presence of various phytochemicals like anthraquinones, soluble tannins, condensed tannins, flavonoids, alkaloids, indole alkaloids, steroidal, alkaloids, saponins, glycosides, resins and terpenoids. The degree of liver protection was analysed by estimating the variation in the levels of AST, ALT, ALP, ACP, total protein and total bilirubin in different groups of experimental rats. They found that the extract is good enough to normalise the otherwise altered levels of AST, ALT, ALP, ACP, total protein and total bilirubin.

3.29. Crossostephium chinensis

Chang *et al.* (2011) substantiated the convalescent nature of medicinal herb *Crossostephium chinensis* whole plant aqueous extract in carbon tetrachloride induced liver damage in rats. The exposure of CCl_4 elevated the levels of SGPT and SGOT, however, the extract of the said plant part brought the levels of these enzymes to normal.

3.30. Portulaca oleracea

Dkhil *et al.* (2011) elaborated the medicinal nature of juice extracted from the whole plant of *Portulaca oleracea* in rats. They highlighted its hepatoprotective nature by estimating the levels of various biomarkers like ALP, AST and ALT in different groups of rats. The investigators achieved the positive result as for as hepatoprotection is concerned.

3.31. Plumbago zeylanica

Kanchana and Sadiq (2011) discovered the protective nature of petroleum ether extract of *Plumbago zeylanica* roots on paracetamol induced liver toxicity in rats. They analysed SGOT, SGPT, ALP, total bilirubin and total protein levels in various groups of rats and compared the results with the group treated with the standard drug silymarin. The results showed the hepatoprotective nature of the *Plumbago zeylanica.*

3.32. Senna alata

Instantaneous conduct of CCl_4 with methanolic extract of leaves of *Senna alata* and fractions (ethyl acetate and butanol) significantly reinstated total protein to near normal levels in rats, while the activities of ALT, AST, ALP, total and direct bilirubin and liver TBARS were significantly dropped off as compared to CCl_4 – treated rats (Kingsley *et al.*, 2011).

3.33. Vernonia cinerea

Leelaprakash *et al.* (2011) studied the restorative nature of ethanolic leaf extract of *Vernonia cinerea* in rats treated with CCl_4. They studied various parameters

during the tenure of their work including mortality, biomarker enzymes like alkaline phosphatase (ALP), problem-solving enzyme markers like aspartate aminotransferase (AST) and alanine aminotransferase (ALT). The outcome of their study showed that leaf extract of *Vernonia cinerea* is helpful in treating the liver toxicity.

3.34. Hippophae rhamnoides

Maheshwari *et al.* (2011) inspected the hepatoprotective behaviour of phenolic rich fraction (PRF) of *Hippophae rhamnoides* leaves on CCl_4 induced oxidative stress in Sprague Dawley rats. They noticed that the phenolic rich fraction actively protected the liver from the rise in AST, ALT and bilirubin in serum.

3.35. Sesamum indicum

Nwachukwu *et al.* (2011) determined the antihepatotoxic effect of methanolic seed extract of *Sesamum indicum* in rats exposed to carbon tetrachloride. A noteworthy increase in the levels of serum markers of hepatic disorder like alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) in CCl_4 control group was observed when compared with the baseline control group. Treatment with extract of *Sesamum indicum* at different doses significantly protected rats from injury as evident by the significant cutback in levels of ALT, AST and ALP in contrast to only CCl_4 treated group.

3.36. Cassia sophera

Wankhade *et al.* (2011) appraised the protective efficacy of ethanolic extract of *Cassia sophera* leaves in rats subjected to paracetamol intoxication. The elevation caused by paracetamol in the levels of AST, ALT, ALP, total protein and total bilirubin was significantly restored when the rats were supplied with the extract of *Cassia sophera* along with paracetamol. The results obtained with the extract were comparable with those obtained by using the standard drug Liv- 52.

3.37. Polygonum bellardii

Adel *et al.* (2012) scrutinized the hepatoprotective activity of *Polygonum bellardii* aerial parts in rats exposed to CCl_4. They confined their study upto the estimation of AST, ALT and bilirubin levels in the serum of different groups of rats and came up with the satisfying outcome.

3.38. Kydia calycina

The hepatoprotective activity of methanol extract of *Kydia calycina* leaves at doses of 250 mg and 500 mg/kg body weight was evaluated in CCl_4 intoxicated rats. The protection offered by the different doses of the plant extract was compared with standard drug Silymarin by calculating the levels of serum ALT, AST, ALP and total bilirubin (Paramashwar *et al.*, 2012).

3.39. Canscora decussate

Akhtar *et al.* (2013) exposed the hepatoprotective activity of *Canscora decussate* against CCl_4 induced liver damage in rabbits using silymarin as control. They selected whole plant material in their study and used methanol and water as the solvents for extraction. Methanolic extract showed significant hepatoprotective effect by lowering serum levels of biochemical parameter such as serum glutamate oxaloacetatetransaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP) and bilirubin as compared to aqueous extract in the rabbits exposed to CCl_4.

3.40. Anogeissus latifolia

Parvathi *et al.* (2013) studied the hepatoprotective activity of *Anogeissus latifolia* leaf and bark extracts (petroleum ether, chloroform and methanol) against carbon tetrachloride induced liver injury in rats. Level of serum markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TB) and total protein were significantly altered in CCl_4 treated rats. The *Anogeissus latifolia* leaf extract at oral dose of 200 and 300 mg/kg for 14 days exhibited significant protective effect by restoring the levels of these parameters to near normal levels in contrast to only CCl_4 treated group of rats.

3.41. Embilica officinalis

Bhuvaneswari *et al.* (2014) assessed the restorative effect of aqueous fruit extract of *Embilica officinalis* in CCl_4 exposed rats. A significant decrease in the level of total protein but a significant elevation in the levels of AST, ALT, ALP and bilirubin was noticed in CCl_4 treated group. However, aqueous fruit extract of *Embilica officinalis* restored the levels of these liver markers towards normal in rats when exposed to CCl_4.

3.42. Mussaenda frondosa

Sambrekar and Patil (2014) examined the hepatoprotective efficacy of alcoholic and aqueous extracts of *Mussaenda frondosa* leaf in intoxicated with Isoniazid. The investigators noticed the significnt change in the levels of serum AST, and ALT, ALP, bilirubin and protein in different groups of experimental rats and came to the conclusion that the alcoholic and aqueous extracts of *Mussaenda frondosa* did possess the genuine protective efficacy.

3.43. Odontonema cuspidatum

Refaey *et al.* (2015) confirmed the hepatoprotective activity of *Odontonema cuspidatum* in rats. The toxicity was created by the intraperitoneal injection of CCl_4. They found that the levels of AST, ALT, ALP and total bilirubin were significantly elevated. However, the methanolic extract of *Odontonema cuspidatum* aerial parts showed significant protection by reducing the pathological conditions of the liver caused by CCl_4.

3.44. Prunus armeniaca

Raj *et al*. (2016) also worked out the hepatoprotective effect of *Prunus armeniaca* in paracetamol intoxicated rats. They found that the extract of the leaves of *Prunus armeniaca* in methanol and water decreased the liver toxicity by decreasing the levels of SGOT, SGPT, ALP and bilirubin.

3.45. Sphaeranthus amaranthoides and *Oldenlandia umbellate*

De *et al.* **(**2017) investigated the in vivo defensive effectiveness of extracts of *Sphaeranthus amaranthoides* and *Oldenlandia umbellate* using rats as the animal model. Their study was based upon the estimation of the levels of SGOT, SGPT, ALP and total bilirubin in various groups of experimental rats. The results they got brought them to the conclusion that the said medicinal plants (whole plant) are worthy enough to decrease the elevated levels of liver markers viz. SGOT, SGPT, ALP and total bilirubin in rats when damaged with CCl_4.

CONCLUSION

Liver toxicity is the main concern first for the patients then for the doctors, scientists and drug manufacturing companies. However, the scientists have put forth different factors causing hepatotoxicity. Scientific medication has its own flaws with regard to their efficacy, side effects and cost, so, the drugs from the plant origin are the alternatives for the treatment of liver ailments. Thus the available literature survey revealed that the plants contain large number of phytochemicals which are decent enough to retrieve the normal health of the liver. However, more pre clinical and post clinical trials need to be done in order to isolate the actual compound accountable for the hepatoprotection.

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