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# Hepatoprotective Activity of Plant Extracts in Non-Human Models: The Toxicants Solvents and Diseased Models-A Review

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## ABSTRACT

The search for an ideal hepatic regenerative agent has led to the modelling of several forms of liver disorders. This involves the usage of various substances in in-vitro and in-vivo systems that are injurious to the human liver in in-vitro and in-vivo systems and then challenged with plants parts extracted with organic and inorganic solvents. Reported view works on hepatotoxicity have been focused on the plant species, this review therefore focused on the toxicants, the solvents for extraction and models used in inducing the hepatotoxicity. Google search, Elsevier and PubMed databases were searched for primary articles from 2005-2022 on hepatotoxicity. In all, 206 articles were retrieved, of which 46 were rejected and 165 were included for the analysis. Authors reported 55 toxicants used in inducing 10 in-vitro and in-vitro models and challenged with 94 different medicinal plants species extracted using 11 different organic and inorganic solvents. Comparatively, tetrachloromethane (CCL4) was the most frequent toxicant 55 of 94 (58.5%) reported plant species while ethanol 25 (45.5%) was the most frequently used solvent for extracting plant phytoconstituents. For the models used in inducing hepatotoxicity, Wistar albino rats 46 of the 55 (83.6%) reported toxicants was the most predominant. The liver is prone to many available toxicants however, phytohepatoregeneration is possible with many medicinal plants which can easily be extracted with common solvents.

## INTRODUCTION

The human liver carries majority of metabolic activities necessary for maintaining homeostasis, cell growth, and repairing degraded, worn-out cells and tissues (Jamuna *et al*., 2018; Eghba *et al*., 2019; Elzwi, 2019). The liver is located in the lower quadrant below the diaphragm (Madrigal-Santillan *et al*., 2014; Al-Snafi *et al*., 2019). The liver is also responsible for synthesizing essential amino acids, fatty acids, vitamins, bile, immunoglobulins which are necessary for proteins synthesis, membrane and immune protection against diseases and infections (Elmansi *et al*., 2017; Maha, 2019; Koubaa *et al*., 2020). The liver also detoxifies harmful products of digestion and respiration such as xenobiotics, toxins and drugs into harmless metabolites for excretion by the kidney and skin (Onojia *et al*., 2019; Olajide *et al*., 2020). Bile produced by the liver also emulsifies fats from food, making it easier for lipase action during digestion (Partel *et al*., 2019). The hepatic portal vein connects the liver to the heart where it receives oxygenated blood from the heart and in turn supply blood with glucose, vitamins, proteins and nutrients necessary to the heart (Usunomena *et al*., 2015; Sani *et al*., 2020; Uchenna *et al*., 2021).

The numerous and multifaceted functions of the liver make it a target for many toxins and pathogens which often results in hepatic diseases such as hepatitis, hepatoma, hepatomegaly, fibrosis, hepatocellular carcinoma, hepatosteatosis and hepatobiliary disorders (Akpanyung *et al*., 2019; Akharaiyu and Okafor, 2021). Therapeutic drugs such as paracetamol, tramadol, rampicin, Adriamycin, caffein as well as environmental pollutants such as carbon tetrachloride produced charged intermediate metabolites which in excess above the body antioxidant capacity results in oxidative stress (Ige *et al*., 2017; Ajiboyea *et al*., 2018; Aly *et al*., 2020). Sustained oxidative stress initiate chain hepatocyte peroxidation of membrane lipids, oxidize sulfhydryl group containing proteins of enzymes and alkylate hepatic cells DNA resulting loss of membrane permeability, inhibition of sensitive enzymes action and necrosis (Elzwi, 2019; Mohammed *et al*., 2020).

Though the idiopathic phase of all liver diseases is cirrhosis or carcinoma, the pathophysiology depends on the toxicant's nature or infectious agent's nature (Zahra *et al*., 2012; Sadashiva *et al*., 2019). Pathogenic microorganisms such as hepatitis B and C viruses usually cause insertional mutagenesis of their genome into hepatic cell DNA (Okaiyeto *et al*., 2018; Okoro, 2020). This mutagenesis results in the translation and transcription of untargeted proteins resulting in undesirable physiological actions (Okaiyeto *et al*., 2018; Okoro, 2020). The infected hepatocytes also display the viral surface antigens resulting in "unself" recognition by the body immune surveillance systems (Senti *et al*., 2016; Okoro, 2020). Chronic hepatic

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infection initiates the expression of proinflammatory and pro-fibrogenic cytokines which cause necrosis, apoptosis and autophagy of infected hepatocytes (Hassan *et al.*, 2015; Oyibo *et al.*, 2020; Nwaogu *et al.*, 2022). Sustained fibrosis result in replacement of degraded hepatocytes with hepatic stellate cells containing extracellular matrix proteins such as collagen and alpha muscle actions which finally lead to cirrhosis (Usmani *et al.*, 2019; Acheampong *et al.*, 2021).

Heavy metals such mercury (Hg), Cadmium (Cd), Arsenic (Ar) and lead (Pb) also react with cellular lipids, carbohydrates and proteins to produce reactive oxygen, nitrogen, superoxide, peroxide and molecular oxygen species beyond the body glutathione and antioxidants enzymes (glutathione peroxidase, superoxide dismutase, catalase) capacity (Chinnula *et al.*, 2018; Ogunmoloye *et al.*, 2022). The loss of antioxidant/free radical balance results in oxidative stress (Dkhil *et al.*, 2013; Iwo *et al.*, 2017). In oxidative stress, the transcription factor nuclear factor kappa Beta NF-kB) is activated in the hepatocyte cytosol and then translocated into the nucleus of the hepatocytes where it causes the gene overexpression of inflammatory cytokines including transforming growth factor 1(TGF-1), tumor necrosis factor-alpha (TNF-alpha), interleukins 1 and 8 (Madrigal-Santillan *et al.*, 2014; Lee *et al.*,2017; Hashem *et al.*, 2019; Ezzat *et al.*, 2020). The profibrogenic cytokines also induce the expression of apoptotic mediators such as caspases-9 and antimitotic cyclins which induced apoptosis of hepatocytes (Immih *et al.*,2022).

Diagnostic and prognostic indicators of liver diseases in clinical and experimental settings rely on liver function markers such as transaminases (alanine transaminase and glutamine transaminase), proteins (globulins and albumins) and pigments (bilirubins) (Olatosin *et al.*, 2014; Mirazi and Karami, 2016; Syvenia *et al.*, 2018). Serum alkaline phosphatase levels indicate membrane disruption (Ashraf *et al.*, 2018). Inflammatory and fibrogenic cytokines TNF-α, transforming growth factor (TGF), nuclear factor kappa B (NF-kB), inducible nitric oxide synthase, cyclooxygenase-2 (COX-2) and interleukins 1,6,8,10 are indicated by PCR quantification of their mRNA levels (Rehab *et al.*, 2016; Ramirez-Marroquin *et al.*, 2019; Salih *et al.*, 2022) as markers of inflammation and fibrogenesis. Oxidative stress is indicated by reduced glutathione level (GSH) and the enzymes glutathione peroxidase, catalase and superoxide dismutase while peroxidation of lipids and proteins are measured using malonaldehyde (MDA), thiobarbituric reactive substances (TBARS), myeloperoxidase (MPO), p-carbonyl proteins, 4-HNE proteins and paraoxonase (Achuba *et al.*, 2019). Mitotic inhibition is indicated by p-cyclins while bax and bcl-2 proteins indicate apoptosis levels (Ameaka *et al.*, 2021). Hepatic steatosis is indicated by mRNA expression of $^{\gamma}$-PPAR and CAT-1 while epithelial-mesenchymal transition (EMT) indicate progression from fibrosis to carcinoma (Elmansi *et al.*, 2017; Ghareeb *et al.*, 2019).

Plant phytochemicals offers promising alternative for the discovery of ideal hepatorestorative agent to replace pharmaceutical drugs which are unavailable, expensive and have harmful side effects (Ameaka *et al.*, 2021). The quest to identify this liver drug have led to the modelling of liver diseases termed hepatotoxicity in animals such as mice, rats and tissues and then challenged with plant parts such as root, leaves, bark, wood, fruit, flowers, puds, sap, fibre and twigs are extracted with organic and inorganic solvents such as alcohols, petroleum ether, water (Sarfo-Antwi *et al.*, 2018; Tokofai *et al.*, 2020).

Hepatotoxicity activity of several medicinal plants have been reported, objective of this review to produce a one-stop collection of these toxicants, their diseased models and solvents.

## MATERIALS AND METHODS

Google scholar, Elsevier and PubMed databases are searched for journals from 2005-2022 on hepatotoxicity using the key words; hepatotoxicity, botanical name of plants and the toxicants. Inclusion into the study is the availability of the plant species, substance for inducing the toxicity, extraction solvent and animal/tissues used in the toxicity. Review articles and journals earlier than 2005 were excluded. Quality checks on the articles downloaded were performed using standard protocols.

### Statistical Analysis

The information was extracted on Microsoft Excel version 2020 (Microsoft Incorporated, New York) and reported as graphs and tables. Discrete data are reported in percentages.

## RESULTS AND DISCUSSION

### Number of Journals Retrieved from Databases

In all, 206 peer reviewed articles were downloaded of which fewer 41 (19.9%) were rejected while majority 165 (80.1%) were included in the review.

### Toxicants Challenged with the Plant Species

In all, 55 toxicants have been reported against 94 plant species. Of these, CCL4 is the most reported toxicant used against 55 plant species, paracetamol/acetaminophen followed with 27 plant species being tested against it. Ethanol (50-100%) has been tested against 12 plants while thioacetamide and dimethylnitosamine are both tested against 7 plants. Galactosamine has been test against 6 plants, with alloxan and lead 5 plants, followed by doxorubicin/Adriamycin and cisplatin 4 plants. Cadmium, aflatoxin B1, Cyclophosphamide, Diclofenac have been tested against 3 plants each while Aluminum chloride, Streptozotocin, 2-acetylaminofluorene (2-AAF), bleomycin (BLM), 7-12, Dimethylbenzanthracene, potassium dichromate/bromate (K2Cr2O7), Hydralazine, ochratoxin A, Rifampin, dimethyl sulfoxide (DMSO) Petroleum has each been challenged against 2 plant species. Lesser studied toxicants include Bromobenzene, Paraben, phosphamide, carbendazim, malathion, Snake Venom,

**Table 1:** Plant species tested against the hepatotoxicants

| Toxicant | Plant Species Tested Against | References |
|---|---|---|
| Carbon tetrachloride (CCL4) | *Azadirachta indica, P. niruri, Phyllanthus lawii, Phyllanthus acidus, Phyllanthus debilis, Vernonia amygdalina, Bidens Pilosa, Taraxacum officinale, Zingibar officinale, Solanum torvum, Syzygium aromaticum, Allium sativum, Carica papaya, Aloe vera, Khaya senegalensis, Piper guineense, Moringa oleifera, Curcuma longa, Arctium lappa, Brassica rap, Bryonia dioica, Bryophyllum calycinum, Convolvulus arvensis, Caesalpinia crista, Canna indica, Capparis spinosa, Capsella bursa-pastoris, Hyoscyamus Species, Hibiscus rosa-sinensis, Helianthus annuus, Glycyrrhiza glabra, Galium verum, Galium aparine, Fumaria parviflora, Fumaria officinalis, Foeniculum vulgare, Euphorbia hirta, Eupatorium cannabinum, Ephedra foliate, Cuscuta planiflora, Cupressus sempervirens, Coriandrum sativum, Cordia myxa, Clitoria ternatea, Cichorium intybus, Sida acuta, Achillea millefolium, Picrorhiza kurroa, Capparis spinosa, Cicer arietinum, Chenopodium album, Celosia cristata, Zanthoxylum zanthoxyloides* | Momoh *et al.*, 2018, Bigoniya and Singh, 2014, 2017, Ezzat *et al.*, 2020, Okroro, 2018, Ajiboyea *et al.*, 2018, Ashraf *et al.*, 2018, Chinala *et al.*, 2018, Lee *et al.*, 2017, Enogieru *et al.*, 2015, Abbas *et al.*, 2017, Shyama *et al.*, 2020, Zahra *et al.*, 2012, Akbari *et al.*, 2019, Akbarizare *et al.*, 2021, Ezzat *et al.*, 2020, Lee *et al.*, 2017, Choudhary *et al.*, 2014, Ghareeb *et al.*, 2019, Elmansi *et al.*, 2017, Acheampong *et al.*, 2021 |
| Paracetamol/ Acetaminophen | *Azadirachta indica, Phyllanthus niruri, Phyllanthus emblica, Phyllanthus niruri, V. amygdalina, Taraxcum officinale, Zingibar officinale, Solanum torvum, Allium sativum, Allium cepa, Moringa oleifera, Momordica charantia, Calotropis procera, Juniperus communis, Hibiscus sabdariffa, Hibiscus cannabinus, Clerodendron inerme, Parkia biglobosa, Saponaria officinalis, Solanum indicum, Maytenus emerginata, Eclipta alba, Aloe vera, Aegle mameloes, Spathodea campanulate, Ficus exasperata* | Ezzat *et al.*, 2020, Momoh *et al.*, 2015, Usmani *et al.*, 2019, Ige *et al.*, 2017, Iwo *et al.*, 2017, Koubaa *et al.*, 2020, Kermani *et al.*, 2020, Farghali *et al.*, 2015, Mahdi *et al.*, 2019, Momoh *et al.*, 2018, Muhammad *et al.*, 2014, Moracles-Gonzalez, 2014 |
| Ethanol | *Azadirachta indica, Phyllanthus amarus V. amygalina, Curcuma longa, Phyllanthus niruri, Syzygium aromaticum, Moringa oleifera, Agrimonia eupatoria, Alhagi maurorum, Anchusa strigose, Zingibar officinale* | Choudhary *et al.*, 2014, Svenia *et al.*, 2018, Ameaka *et al.*, 2021, Singh *et al.*, 2012, Innih *et al.*, 2022, Maha, 2019, Hashem *et al.*, 2019, Kermani *et al.*, 2020 |
| Thioacetamide | *Phyllanthus niruri, Taraxacum officinale, Zingibar officinale, Curcuma longa, Allium sativum,Moringa oleifera, Crotalaria juncea* | Shyama *et al.*, 2020, Sani *et al.*, 2020, Rehab *et al.*, 2016, Sadashiva *et al.*, 2019, Madrigal-Santillan *et al.*, 2014, Chinnala *et al.*, 2018 |
| Galactosamine | *Phyllanthus maderaspatensis, Bidens Pilosa, Taraxacum officinale, Curcuma longa, Brassica nigra, Cistanche tubulosa* | Abbas *et al.*, 2017, Zahra *et al.*, 2012, Muhammad *et al.*, 2015, Shyama *et al.*, 2020 |
| Dimethylnitrosamine (DMN) | *Vernonia amygdalina, Zingiber officinale, Astragalus hamosus, Bauhinia variegate, Cynodon dactylon, Citrullus colocynthis, Spathodea companulata* | Mahdi *et al.*, 2019, Oyibo *et al.*, 2021, Momoh *et al.*, 2018, Uchenna *et al.*, 2021, Nwaogu *et al.*, 2022 |
| Alloxan | *Azadirachta indica, Vernonia amygdalina, Curcuma longa, Moringa oleifera, Paullinia pinnata* | Momoh *et al.*, 2015, Momoh *et al.*, 2018, Koubaa *et al.*, 2020, Salih *et al.*, 2022 |
| Lead | *Phyllanthus fraternus, Allium sativum, Zingiber officinale, Curcuma longa, Moringa oleifera* | Kermani *et al.*, 2020, Eghba *et al.*, 2019 |
| Cisplatin | *Azadirachta indica, Cuminum cyminum, Phyllanthus emblicus, Silymarin* | Iwo *et al.*, 2017, Tokofai *et al.*, 2021, Ogunmoloye *et al.*, 2022 |
| Cadmium | *Trema orientalis, Solanum torvum, Syzygium aromaticum* | Innih *et al.*, 2022, Olajide *et al.*, 2020 |

| | | |
|---|---|---|
| Aflatoxin B1 | *Phyllanthus amarus, Calendula officinalis, Parkia biglobosa* | Farghali *et al.*, 2015, Ajiboye *et al.*, 2014 |
| Cyclophosphamide | *Phyllanthus fraternus, Hypericum triquetrifoliu, Eucalyptus globulus* | Usmani *et al.*, 2019, Ghareeb *et al.*, 2019, Ige *et al.*, 2017 |
| Doxorubicin/ Adriamycin | *Zingiber officinale, Curcuma Longa, Coconut Oil, Vernonia amygdalina* | Lai *et al.*, 2021, Ezzat *et al.*, 2020, Ige *et al.*, 2017 |
| Diclofenac | *Curcuma longa, Glycyrrhiza glabra, Moringa oleifera* | Ashraf *et al.*, 2018, Hassan *et al.*, 2015, Sarfo-Antwi *et al.*, 2018 |
| Streptozotocin | *Moringa oleifera, Vernonia amygdalina* | Ajiboyea *et al.*, 2018, Enogieru *et al.*, 2015 |
| Bleomycin (BLM) | *Curcuma longa, Juglans regia* | Elzwi, 2019, Yankah *et al.*, 2019 |
| 7-12, Dimethylbenzanthracene | *Turmeric, Garlic* | Choudhary *et al.*, 2014, Chinnala *et al.*, 2018, |
| Potassium dichromate/ bromate (K2Cr2O7) | *Moringa oleifera, Allium cepa* | Elmansi *et al.*, 2017, Akbarizare *et al.*, 2020, |
| Hydralazine | *Syzygium aromaticum, Heliotrpium undulatum* | Patel *et al.*, 2019, Lee *et al.*, 2017 |
| Ochratoxin A | *Allium sativum, Withania somnifera* | Jamuna *et al.*, 2018 |
| Rifampin | *Azadirachta indica, Carthmus tinctorius* | Akbari *et al.*, 2019, Ezzat *et al.*, 2020 |
| Dimethyl sulfoxide (DMSO) | *Citrus limon, Citrus aurantifolia* | Dkhil *et al.*, 2013, Acheampong *et al.*, 2021, |
| Petroleum | *Vernonia amygdalina, Daucus carota* | Zahra *et al.*, 2012, Achuba *et al.*, 2020 |

Eimeria papillate, DMBA, acetylaminofluorene (2-AAF), tert-butyl hydroperoxide (t-BH), PCB, Theobromine, Permethrin, sodium dichromate, nitrobenzene (NB), Diazinon, mercuric chloride, Acrylamide, Methotrexate, N, N-dimethylformamide (DMF) which have been tested against 1 plant species. Table 1 indicates the toxicants and the plant species tested against.

**Solvents Used for Extraction Plants**

In the accepted articles, authors used 11 chemicals to induce hepatotoxicity including Ethanol, Aqueous, Methanol, Phenol, ethylacetate, Petroleum ether, chloroform, hexane, Oil, fermented form, acetone to extract the plant phytochemicals. In 25 toxicants used to induce liver diseases, ethanol was the solvent used for extracting the plant parts while methanol was the solvent in 16 toxicants tested and distilled water (13 toxicants) as indicated in figure 1.

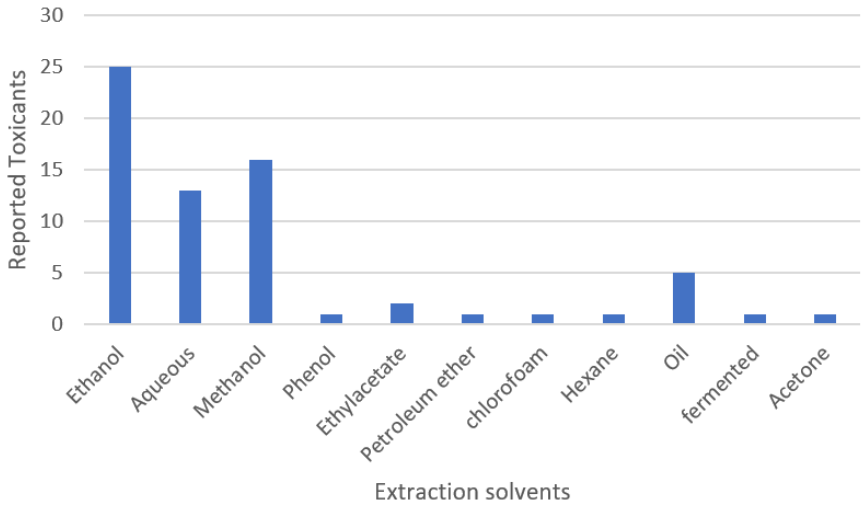


**Figure 1:** Solvents used in extracting phytochemicals tested against toxicants

**In-Vitro and In-Vivo Models Liver Toxicity were Induced with the Toxicants**

Hepatotoxicity was induced in 10 in-vitro and in-vivo models including Wister Albino rats, Sprague-Dawley rats, HepG2 cell culture line, mice, rabbits, clone-9 cells, broiler chicken, goat hepatocytes, guinea pigs, Swiss albino rats and then tested against the extracted plant phytochemicals. Hepatoxicity was induce in Wistar albino rats using 46 different toxicants followed by Sprague-Dawley rats and Hep G2 cell cultures with 6 different toxicants each. Toxicity of hepatocytes was also reported in mice models using 4 different toxicants while 3 separate toxicants were used to induced liver diseases in Swiss albino rats. Rabbits, clone-9 cells, broiler chicken, Goat

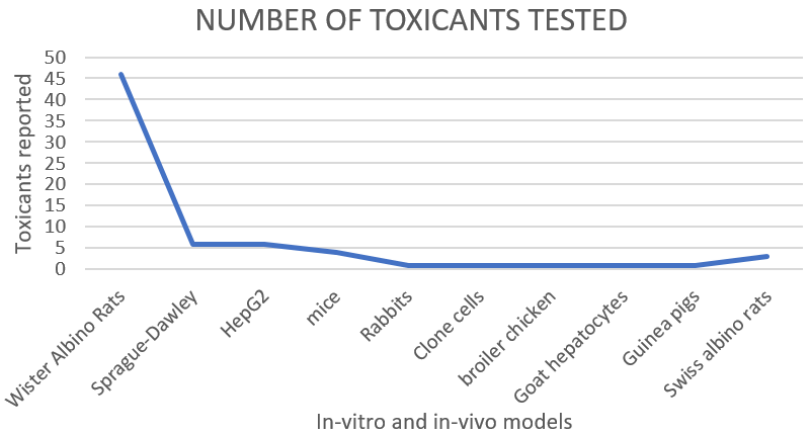


**Figure 2:** In-vitro and in-vivo models used to model hepatotoxicity

hepatocytes, Guinea pigs were induced with liver diseases using a single toxicant each as indicated in Figure 2.

## DISCUSSION

The review indicates that CCL4 is most prevalent toxicant 55/94 plant species (58.5%) with ethanol being the most solvents 25/55 toxicants (45.5%) and Wistar albino rats being the commonest 46/55 toxicants (83.6%) in-vivo hepatotoxicity inducing model. Despite being a known respiratory inhibitor as it binds and oxidise heme in haemoglobin (Talluri *et al*., 2018), CCL4 now banned is one of earliest discovered toxicant (Enogieru *et al*., 2015; Innih *et al*., 2022). CCL4 is less expensive and can be obtained easily for study purposes. Due to its availability in the environment from fridges and industrial chemicals, CCL4 hepatotoxicity also represent a real-time risk of liver diseases.

Phytochemical compounds are organic and therefore dissolve on the principle of polar substance dissolve in polar solvents (Senti *et al*., 2016). Comparatively, ethanol comes next to phenol in terms of polarity and will therefore yield high phytochemicals. Attenuating hepatotoxicity induced by oxidative stress has been dose-dependent (Oboma *et al*., 2018, Momoh *et al*., 2018). Therefore, the higher the phytochemical yield, the more effective oxidative stress remediation. In a comparative study, Mahdi *et al*. 2019, reported that hydro-ethanolic had better hepatotoxicity than same concentration of methanol, chloroform and ether account of solvent polarity. It is also reported that, moderate ethanol concentrations 50-70% had better hepatoprotective activity that lesser concentration and higher concentrations (Shah *et al*., 2016). At lower concentration, phytochemical yield is less while at higher concentration, cellular parts and toxic antinutrients are extracted which pose further hepatic harm.

Wistar albino rats are more adaptable to environmental conditions with less case fatalities during experimentation. They rapidly progenerate making them less expensive and available for research purposes (Ajiboyea *et al*., 2018). This adaptability to human weather conditions also make it suitable to real human hepatic conditions.

## CONCLUSION

Many toxicants have been reported to induce liver diseases in various models, however, several medicinal plants have been reported to ameliorate these induced hepatic diseases. Medicinal plants therefore present hope for the discovery of ideal hepatorestorative agents that will be less expensive largely due to their ability to dissolve in common solvents like ethanol.

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