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A REVIEW: HERBAL MEDICINES AND SCREENING MODELS FOR HEPATOPROTECTIVE AGENTS

Pratiksha Kothari*, Ashvini Andhale and Santosh Waghmare

Loknete Shri Dadasaheb Pharate Patil College of Pharmacy, Mandavgoan Pharata, Tal-Shirur, Dist.-Pune. Maharashtra.

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***Corresponding Author**
Pratiksha Kothari
Loknete Shri Dadasaheb Pharate Patil College of Pharmacy, Mandavgoan Pharata, Tal- Shirur, Dist.-Pune. Maharashtra.

ABSTRACT

Liver is the largest gland present in human body. The function of this vital organ includes storage of glycogen, vitamins and minerals, enzyme activation, metabolism of carbohydrate, proteins and detoxification as well as purification process. Liver regulates chemical levels in blood and forms excretory material that is bile. All the blood leaving the stomach and intestine passes through liver. Chronic alcohol consumption, exposure to toxic chemicals like paracetamol, tetracycline, anti-TB drugs, NSAIDS, chemotherapeutic agents damage the hepatocytes. Liver diseases are major health and challenging to health care professions and pharmaceutical industry. Therefore there is need to study the hepatoprotective agents. Modern medicine have provided many medicaments that cure liver diseases but compared to this herbal medicine is preferred due to its cost effectiveness as well as minimal side effects and safe approach. The aim of this review is compiling information of different medicinal plants with their hepatoprotective activity on various models of hepatotoxicity.

KEYWORDS: Liver, Hepatotoxic agents, Medicinal herbs as hepatoprotective agents, Screening models.

INTRODUCTION

The Liver is the largest gland in a human body, situated in the right side of upper abdominal cavity. The cells of the liver called hepatocytes plays vital functions like;

1. Synthesis of proteins, biles,
2. Stores glycogen, vitamins, iron,
3. Metabolizes toxic chemicals and drugs

Drug metabolism is a process of detoxification in which a substance is chemically modified into a less toxic form under the influence of enzymatic system.

Medicinal plants play a key role in the human health care. About 80% of the world population relies on the use of traditional medicine. The traditional medicine includes Ayurveda, Siddha and Unani. Liver damage is very common since liver has to detoxicate many toxic substances. Most of the hepatotoxic chemicals damage liver cells by producing reactive species which form covalent bond with the lipids of the tissue. Due to excessive exposure to hazardous chemicals, sometimes the free radicals generated are so high that they overpower the natural defensive system leading to hepatic damage and cause jaundice, cirrhosis and fatty liver. Production of the reactive species depletion manifests in tissue thiol depletion, lipid peroxidation, plasma membrane damage etc., culminating into severe hepatic injury. The agents which are capabale for protecting liver from these hepatotoxins are called as Hepatopreotective Agents. For this reason, researches have been developed in the search of natural and/or synthetic compounds with hepatoprotective activity. The development of new pharmaceuticals consists of a variety of steps, going from the discovery of pharmacological side effects in cellular and animal models, to prove its efficacy and safety in human beings. In vivo and ex vivo test models are used to evaluate hepatoprotective activity. These include ability of the drug to prevent or cure hepatic toxicity in cellular cultures, organs or in experimental animals (rats, mice, *etc*.).[1-4]

Hepatotoxins and Their mechanism of hepatotoxicity

Chemical agents causing hepatotoxicity

Inorganic chemical agents

Metals and Metalloids

Antimony, Arsenic, Beryllium, Bismuth, Boron, Cadmium, Chromium, Cobalt, Copper, Iron, Lead, Manganese, Mercury, Gold, Phosphorous, Selenium, Tellurium,

Thallium, Zinc, Hydrazine derivative, Iodides 22, 23.

Organic chemical agents

Natural: Plant toxins

Albitocin, Cycasin, Nutmeg, Tannic acid, Icterogenin, Pyrrolidizines, Saferole, Indospicine.

Mycotoxins: Aflatoxins, Cyclochlorotine, Ethanol, Luteoskyrin, Griseofulvin, Sporidesmin, Tetracycline and Other Antibiotics.

Bacterial toxins: Exotoxins (C.diphtheria, Clostridium botulinus), Endotoxins, Ethionine.

Synthetic: Haloalkanes and Haloolephins, Nitroalkanes, Chloroaromatic compounds, Nitro-aromatic compound, Organic Amines, Azo compounds, Phenol and derivatives, Various other organic compounds.[5-7]

Table no. 1: Medicinal agents causing hepatotoxicity.

Category of Drug	Examples
Neuropsychotroics	Hydrazine, Tranylcypromine, Anticonvulsants, Antidepressants.
Anti-inflammatory and anti-muscle spasm agent	Cinchopen, Cholchicine, Ibuprofen, Salicylates, Indomethacin.
Antineoplastic	L-Asparaginase, Azacytidine, Methotrexate, 6-Mercaptopurine, Chlorambucil, Clavicin
Antimicrobials	Clindamycin, Novobiocin, Penicillin, Tetracycline, Sulfonamide, Amodiaquine, Isoniazid, Rifampin.
Hormonal derivatives and other drugs used in endocrine disease	Acetohexamide, Azepinamide, Carbutamide, Tolbutamide.
Antidiabetics	Glibenclamide, Metformin, Glimepride

1. **Carbon tetrachloride:** Trichloromethyl free radical in the body attacks the polyunsaturated fatty acids of the membrane of endoplasmic reticulum and leads to the hepatotoxicity. Carbon tetrachloride poisoning leads rapidly to cessation of movement of large quantities of triglycerides from the liver to the plasma leading to fatty liver. If the damage is severe it leads to an abnormal increase in liver enzymes followed by hepatocellular necrosis. There is an influx of monocytes into the liver during acute and chronic CCl_4 induced hepatotoxicity causing an increase of Reactive Oxygen Species (ROS) production and a rise in Kupffer cell leukotriene production in the liver leading to imbalance between cytoprotective and cytotoxic prostanoids.

2. **Paracetamol:** It is activated by cytochrome P450 to a reactive metabolite that covalently binds to protein. The reactive metabolite responsible for hepatotoxicity is N-acetyl-p-benzoquinone imine which reacts with N-acetyl cysteine. Various mechanisms leading to paracetamol toxicity includes -

a. Increased formation of superoxide anions which cause lipid peroxidation (oxidative stress) via hydrogen peroxide formation.
b. Decreased glutathione concentrations in centrilobular cells.

3. **D-galactosamine:** Galactosamine administration induces an inflammatory response in liver that biochemically and histologically resembles viral hepatitis. A single

administration causes hepatocellular necrosis and fatty liver. It causes appearance of specific lesions in liver cells, characterized by inhibition of nuclear RNA and protein synthesis.

4. **Thioacetamide:** Thioacetamide, originally used as a fungicide is a potent hepatotoxic and is bioactivated by CYP450 and flavin containing monooxygenase (FMO) systems to sulfoxide and sulfone metabolites, which causes centrilobular and liver necrosis. Thioacetamide interferes with the movement of RNA from the nucleus to cytoplasm which may cause membrane injury.[4,7,8,9]

Herbal plants as hepatoprotective agents

Traditional herbal medicines are generally preferred to cure liver disorders. Some of herbs like *Andrographis paniculata*, *Cyperus longurs* and *Asteracantha longifolia* are known to possess therapeutic efficacy of cure liver diseases. Following are the hepatoprotective plants

***Taraxacum officinale*:** Also called as Dandelion, is used as a folkloric medicine for the treatment of liver and kidney disorders.

Wilkstroemia indica: It is a Chinese herb and has been used to treat in patients suffering from hepatitis B. A dicoumarin, daphnoretin are the active constituents of the herb. The drug has shown to suppress HbsAG in Hep3B cells. It activates protein kinase C.

Tephrosia purpose: In animal models, it offered protective action against carbon tetrachloride and D-galalactosamine poisoning. The roots, leaves and seeds contain tephrosin, deguelin and quercetin.

Glycyrrhiza glabra: It is mainly used in Japan for the treatment of patients with liver diseases. Reduction of serum aminotransferases and long-term usage of glycyrrhizin prevents development of hepatocellular carcinoma in chronic hepatitis.

***Phyllanthus niruri/Phyllanthus amarus*:** They both possess hepatoprotective activity. Geetha et al., (1992) found improved liver function in patients treated with Phyllanthus amarus bringing about a significantly faster normalization of biochemical changes than control groups.

Bupleurum falcatum: Saiko, a crude obtained from the roots of Bupleurum falcatum has been used for the treatment of hepatobiliary diseases. Saikosaponninsare responsible for the alleviation of liver dysfunction.

Andrographis paniculata: Also called as Kalmegh and grows wildly in India. It is used against acute hepatitis induced by carbon tetrachloride, paracetamol and D-galactosamine as is evident from morphological, biochemical and functional parameters.

Curcuma longa: Hepatoprotective activity of Curcuma longa and curcuminoids against carbon tetrachloride and galactosamine induced liver damage has been reported. Curcumin also inhibit the activity of glutathione-s-transferase.

Pistacia lentiscus: Aqueous extract of Pistacia lentiscus shows antihepatotoxic activity by reducing the activities of ALP, ALT, AST and the level of bilirubin.

Garcinia kola: Active constituent,Kolaviron recoupe the CCl4 induced liver damage. Kolaviron also protects erythrocyte membrane from free radical attack on both lipids and proteins.

***Wedelia calendulacea*:** The active constituent wedelolactone possess significant hepatoprotective activity. The leaves of Wedelia calendulacea shows significant protection against paracetamol induced hepatocellular injury.

***Apium graveolens*:** Methanolic extract of Apium graviolens confiems the hepatoprotective activity. It is monitored by several function tests.

***Boerhaavia diffusa linn*:** The choloroform and methanolic extract of the roots and aerial parts of Boerhaavia diffusa shows hepatoprotective activity against carbon tetrachloride, paracetamol and D-galactosamine intoxication in experimental rats.

***Eclipta alba*:** It shows antihepatotoxic activity against carbon tetrachloride, D-galactosamine and phalloidin induced toxicity against rat hepatocytes. These activities are due to the regulation of hepaticmicrosomal drug metabolising enzymes.

Carica papaya: Ethanolic and aqueous extract of Carica papaya was used for antihepatotoxic activity against CCl4 induced liver damage by using biochemical parameters such as AST, ALT, ALP, total bilirubin and GGT.

***Myristica fragrans*:** It shows potent hepatoprotective activity. It suppressed LPS/D-GalN-induced enhancement of serum TNF-alpha concentrations and hepatic DNA fragmentation in mice.

Solanum nigrum: Also celled as kakamachi. Aromatic water extracted from the drug is widely prescribed by herbal vendors for liver disorders. Although clinical documentation is scare as far as hepatoprotective activity is concerned, but some traditional practitioners have reported favorable results with powdered extract of the plant

Orthosiphon stamineus: The hepatoprotective activity of the methanol extract of *Orthosiphon stamineus* was assessed in paracetamol induced hepatotoxicity rat model.

Change in the levels of biochemical markers such as AST, ALT, ALP and lipid peroxides were assayed in both paracetamol treated and control (untreated) groups. Treatment with the methanolic extract of *O. stamineus* leaves (200 mg/kg) has accelerated the return of the altered levels of biochemical markers to the near normal profile in the dose dependent manner.[10-18]

Table no. 2: Some siddha medicinal plants used as hepatoprotective agents.[19-25]

Name of plant	Part used	Extract	Hepatotoxic agent used	Remark
Aerva lanata	Fresh plants	Hydroalcoholic extract	Paracetamol	Reduced in serum enzymes ALT, AST, ALP and bilirubin
Allium cep	Bulbs	Methanolic extract	Paracetamol	Reduced in the level of ALT and total serum bilirubin in dose dependent. It reduced AST,ALP, LDH level
Amarantus spinosus	Whole plant	50% ethanolic extract	CCl4	SGOT, SGPT, ALP &TB.The presence of flavonoids andphenolics compound may be responsible
Azadirachata indica	Leaves	Aqueous extact	Paracetamol	Reduced in Levels of AST, ALT & GGT
Cassia fistula	Leaves	n-heptane	Paracetamol	Lowering the levels of SGOT and SGPT, bilirubin and ALP
Emblica officinalis	Fruits	50% ethanolic extract	Rifampicin,isoniazide & pyrazinamide	Reversal of serum enzyme activity i.e. (AST,ALT, ALP, bilirubin) LPO & recovery of GSH content. CAT &GSH-Px activities were restored.

Table no. 3: Well known herbal Products and Their composition.[10,25]

Herbal Products	Composition
Liv-52 M/S The Himalaya Drug Co., Makali, Bangalore.	Punarnava, Vidanga,Haritaki, Parpata Guduchi, Bringaraj, Daruharidra, Chitraka, Amlaki
Livotone M/S East India Pharm. Works., Calcutta	Kalmegh, Ajmod, Talmakhana, Raktarohida, Methi, Kurchi
Stimuliv M/S Francho - Indian Pharma-ceuticals Ltd., Bombay	Kalmegh, Bringaraj, Pitpapra
Tefroli	Kalmegh, Bringaraj, Sarponkha,Tulsi, Harde

(M/S TTK Pharm Madras)	
Hepatogard M/S Surajmani Enterprises A-1, Daman, Somnath Road , Dabhei Daman	Kutki, Kalmegh, Bhumyamlaki, Punarnava, Neem, Triphala, Bringaraj, Sunti, Pippali
Livomyn M/S Charak Pharmaceuticals Ltd,Samalkha	Vasaka, Brhati, Rohituk, Punarnava, Bhumyamlaki, Katuki, Guduchi

Screening Models Used For Hepatoprotective Agents:

They are classified as

1. In vitro models
2. Ex-vivo model
3. In vivo studies

1. In-vitro models

Fresh hepatocytes, primary hepatocyte cultures and immortalized cell lines are used to measure the hepatoprotective effect. It is possible to establish action mechanisms in these models Primary hepatocyte cultures have the characteristic of maintaining normal metabolic liver properties, but it is not possible to maintain them for a long time. On the other hand, cell lines maintain their properties stable for a long time and can be cryopreserved, but immortalized or carcinogenic lines may differ in biochemical and metabolic aspects from normal cells.

In order to evaluate protection, parameters like transaminase liberation, cell multiplication, morphology, macromolecular synthesis, oxygen consumption, *etc.*, are measured.

Advantages

1. They are quick tests (between 2–3 testing days)
2. They require small amounts of the test substances (milligram range) and the experimental conditions may be strictly controlled, different samples may be analyzed in the same test.
3. They are cheap tests and there is little variability; therefore they are considered a reproducible test.

Disadvantages

1. Cells do not function independently in the organism; on the contrary, they form close and complicated nets with each other and with the extracellular matrix; therefore, this should be taken into consideration when interpreting *in vitro* data and should be verified with *in vivo* systems.

2. Isolated cells as well as cell lines have an elevated cell differentiation rate due to the loss of natural environment. The substances tested do not go through the absorption and distribution processes, which occurs in the organism. There is little to no cell-to-cell interaction and there is no complexity proper of the organ.

2. Ex-vivo model

Precision cut liver slices (PCLS) are an *ex vivo* tissue culture which imitates multicellular characteristics of *in vivo* organs. Cellular interaction and spatial disposition remain intact in this model, with the possibility of performing morphological studies. Liver slices have the characteristic of functionally maintaining metabolizing enzymes and biliary canaliculus; they have proven to be a valid *ex vivo* system to study metabolism and liver damage and function as a bridge between *in vivo* systems and cell cultures.

Isolated perfused livers represent a model combining *in vitro* characteristics under *in vivo* circumstances. The first model was developed in porcine livers and later the livers of smaller animals (rats, mice and rabbits). This model preserves the tridimensional structure as well as the cell-to-cell interactions with the possibility of collecting bile in real time. If blood is used as a perfusor liquid, then hemodynamic parameters may be studied.

Advantages

1. Have low cost, reproducible models.
2. In PCLS the number of experimental animals is reduced, also the model can be developed with human organs.

Disadvantages

1. The bile flow and functional parameters, such as portal flow, cannot be analyzed.
2. There is poor diffusion of oxygen nutrients to the more internal cells, and even with the development of new means of culture, the viability of the slices remains short (8–10 Days).
3. In small labs, because of space and budget, the best option is the development of perfused rat liver; however, there are significant differences in the size, function and geometry of the murine liver compared to the human.

3. In-vitro Model

This model has been widely used; through this model we are able to determine the protection mechanism. The damage produced in experimental animals due to known dosage administration of different hepatotoxins and the magnitude of the damage and/or protection is determined by the different biochemical and metabolic markers, as well as histopathological determinations**.**

Advantages of *in vivo* models

1. It is the model with the highest degree of correlation with what occurs in humans and all biochemical and histopathological parameters can be measured.
2. They let us take into account the possible effects of the immune and central nervous systems in the development of hepatic diseases.

Disadvantages of *in vivo* models

1. They require a large number of animals, and usually the studies are developed for long periods of time, increasing ethical and financial aspects.
2. There is an inter-individual variation, and even though models imitating the different hepatic diseases have been developed, there are relevant differences in the molecular pathogenesis between the model and human species.
3. They require a larger sample size to perform the experiment which may be a limiting factor, especially when analyzing natural products.[12,28,32]

CONCLUSION

The present review reveals plant extract with hepatoprotective agents used in folk medicines against toxic chemicals that cause liver injury. These plants may offer new alternatives to the limited therapeutic options that exist at present in treatment of liver diseases or symptoms related to its which would be very helpful for future studies. The study also identified glycosides, flavonoids, triterpenes and phenolic compounds used as hepatoprotective agents.

The present study reveals plant extracts with hepatoprotective properties against toxic chemicals that cause liver injury, seeming to validate their use in folk medicine. These plants may offer new alternatives to the limited therapeutic options that exist at present in the treatment of liver diseases or their symptoms, and they should be considered for future studies.

The study also identified glycosides, flavonoids, triterpenes and phenolic compounds as classes of compounds with hepatoprotective activity. The potent hepatoprotective activities of the chemically defined molecules isolated from natural origins represent an exciting advance in the search for effective liver protective agents, especially now, when there is an urgent need for new innovative drug leads.

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