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Research Article

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Hepatoprotective nature of phytoextracts against hepatotoxin induced animal models: A review

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ABSTRACT

Liver is the largest vital organ in human body and plays a major role in various metabolism and excretion of xenobiotics within the body. Liver dysfunction is a foremost health problem that challenges not only health care professionals but also the pharmaceutical industry as more than 900 drugs are implicated in case of liver injury. Hepatotoxicity is caused by various toxic substances and certain pharmaceutical drugs which produce liver injury such as-carbon tetrachloride, thioacetamide, high doses of acetaminophen, anti-tubercular drugs, few chemotherapeutic agents etc. The existing modern synthetic drugs to treat liver disorders in this condition also cause furthermore liver damage/complications. Therefore, many herbal drugs from natural origin have become increasingly popular and their use is wide spread. These herbal medicines have been used in the treatment of liver diseases for a long time because of their antioxidants properties and tissue protective nature. Extensive researches have been carried out on medicinal plants; however, only few herbal plants have attracted the interest of researchers, to evaluate them for better protective/therapeutic agents for hepatoprotective against chemical induced liver toxicity. Various preclinical investigations have proved that the efficacy of medicinally important plants in the treatment of liver diseases/disorders. Hence, this article provided valuable evidence to the knowledge of investigated medicinal plants; especially those medicinal plants are suitable for hepatoprotective and therapeutic nature against liver toxicity.

Key words: Hepatoprotective, Liver Injury, Carbon tetrachloride, Hepatotoxicity, Medicinal plants.

INTRODUCTION

Liver is the most important organ that involves in various crucial role in regulating metabolic pathways, other biochemical and physiological processes. It is also involved in various vital functions including metabolism, secretion, excretion, storage, mainly detoxicate toxic substances and synthesize useful principles [1]. It comprise with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction [2]. The role played by this organ in the removal of substances from the portal circulation makes it susceptible to first and persistent attack by offending foreign compounds, culminating in liver dysfunction [3].

Liver cell injury caused by various toxicants such as certain chemotherapeutic agents, carbon tetrachloride-ride, thioacetamide etc., chronic alcohol consumption and microbes is well-studied. Enhanced lipid peroxidation during metabolism of ethanol may result in development of hepatitis leading to cirrhosis. Drug-induced liver toxicity is a very common cause of liver injury during medication. It accounts for approximately one-half of the cases of acute liver failure and mimics all forms liver diseases of acute and chronic stages [4]. The first line drugs used for tuberculosis therapy such as Isoniazid and rifampicin are associated with severe hepatotoxicity [5]. The rate of

hepatotoxicity has been reported to be much higher in developing countries compared to that in developed countries with a similar dose schedule [6]. Based on the WHO health reports [7], anti-tuberculosis drugs effectively induced hepatotoxicity in worldwide; hence, researchers having difficulties in systematic steps for prevention and management of anti-tuberculosis drugs and other related drugs induced hepatotoxicity. All western medicines have produced significant unwanted side effects against human health in particularly liver toxicity. Hence, researchers are looking effective therapeutic drugs against drug induced liver toxicity.

Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. The association of medical plants with other plants in their habitat also influences their medicinal values in some cases. Since time immemorial, mankind has made the use of medicinal plants in the treatment of various ailments. Recently, various medicinal plants and their phytoextracts/active bioactive compounds have shown plenty of medicinal properties including antioxidant [8, 9], anti-inflammation [10], anti-cancer [11], anti-microbial [12, 13], anti-diabetes [14, 15], anti-nociceptive action [16] etc.

Medicinal plants play a key role in human health care for decades. About 80% of the world population relies on the use of traditional medicine, which is predominantly based on plant material. Scientific pre-clinical studies available on medicinal plants indicate that promising phytochemicals can be developed for many health problems such as anti-diabetes, anti-cancer, anti-inflammation [17-22]. Among different sources of natural products, plants have been a source of chemical substance, which serves as drugs in their own right or key ingredients in formulation containing synthetic drugs. One of the important and well-documented uses of plant-products is their use as hepatoprotective agents. Hence, there is an ever increasing need for safe hepatoprotective agent without any side effects.

Table-1: A retrospective database of plant exhibiting hepatoprotective activity – established through systemic studies.

Scientific name	Parts Utilized	Extract Solvent	Investigated – Hepatotoxic model	References
Adoxaceae Viburnum tinus L.	Leaves	Aqueous / Methanol	Carbon tetrachloride induced	[25]
Aegle marmelos	Leaves	Ethanol	Alcohol	[26]
Aframomum longiscapum	Seed	Aqueous	Sodium Arsenite and Ethanol	[27]
Allium paradoxum	Aerial parts/ Bulbs	-	Carbon tetrachloride	[28]
Amomum xanthioides	Whole part	Aqueous	Dimethyl nitrosamine	[29]
Andropogon muricatus	Roots	Methanol	bile duct ligation-induced liver fibrosis	[30]
Andrographis lineate	Leaves	Aqueous / Methanol	Carbon tetrachloride	[31]
Andrographis paniculata	Leaves	Alcohol	Carbon tetrachloride	[32]
Anisotes trisulcus	-	Ethanol	Carbon tetrachloride	[33]
Annona squamosa	Whole plant	Alcohol	Diethylnitrosamine	[34]
Apium graveolens	Seeds	Methanol	Paracetomol + Thioacetamide	[35]
Acanthopanax senticosus	-	-	Carbon tetrachloride and Paracetomol	[36]
Artemisia vulgaris	Aerial	Aqueous / Methanol	D-galactosamine + Lipopolysaccharide	[37]
Artemisia iwayomogi	-	Ethyl acetate	Carbon tetrachloride	[38]
Artemisia capillaris	-	Ethyl acetate	Carbon tetrachloride	[38]
Anoectochilus formosanus Hayata	Whole plant	Aqueous	Carbon tetrachloride	[39]
Asteracantha longifolia	Whole plant	Aqueous	Carbon tetrachloride and Paracetomol	[40]
Achyrocline satureioides	Aerial	Aqueous	Bromobenzene	[41]
Alchornea cordifolia	Leaves	Ethanol	Paracetomol	[42]
Acacia catechu	Bark	Ethyl acetate	Carbon tetrachloride	[43]
Beta vulgaris	Root	Ethanol	Carbon tetrachloride	[44]
Bauhinia racemosa	Bark	Methanol	Paracetomol + Carbon tetrachloride	[45]
Bauhinia variegata	Bark	Alcohol	Carbon tetrachloride	[46]
Borreria hispida		Methanol	Paracetomol	[47]
Bixa orellana	Seeds	Methanol	Carbon tetrachloride	[48]
Coronopus didymus	Whole plant	Aqueous	Carbon tetrachloride	[49]
Commiphora opobalsamum	Aerial	Ethanol	Carbon tetrachloride	[50]
Caesalpinia sappan	Heartwood	Methanol /Aqueous	Carbon tetrachloride	[51]
Cajanus cajan	Leaves	Methanol	Alcohol	[52]
Carum copticum	Seeds	Aqueous / Methanol	Carbon tetrachloride and d-galactosamine	[53]
Cassia roxburghii	-	Methanol	Ethanol + Carbon tetrachloride	[54]
Cleome viscosa	Leaves	Ethanol	Carbon tetrachloride	[55]
Casuarina equisetifolia	Leaves, Bark	Methanol	Carbon tetrachloride	[56]
Chamomile recutita	-	Ethanol	Paracetomol	[57]
Careya arborea Roxb.	Bark	Methanol	Carbon tetrachloride	[58]
Cyperus articulatus	Whole parts	Methanol	Paracetomol	[59]

Cichorium endivia L.	Leaves	-	Tertiary Butyl Hydroperoxide (TBHP)	[60]
Cichorium intybus L.	Seeds	Alcohol	Carbon tetrachloride	[61]
Cichorium intybus	-	Polyphenolic extracts	Thioacetamide	[62]
Cissampelos pareira	Root	Hydro-alcoholic	Carbon tetrachloride	[63]
Cleome viscosa	Seeds	-	Carbon tetrachloride	[64]
Clitoria ternatea	Leaves	Methanol	Paracetomol	[65]
Coccinia grandis Linn	-	Alcoholic	Carbon tetrachloride	[66]
Combretum quadrangulare	Leaves	Methanol	D-galactosamine	[67]
Cuscutae semen	Seeds	Aqueous	Dimethynitrosamine	[68]
Crassocephalum crepidioides	Whole plant	Aqueous	D-galactosamine + Lipopolysaccharide + Carbon tetrachloride	[69]
Desmodium triquetrum	Leaves	Ethanol	Carbon tetrachloride	[70]
Diospyros malabarica	Bark	Methanol	Carbon tetrachloride	[71]
Emblica officinalis	Fruits	Hydro-Alcoholic	Anti- Tuberculosis drug	[72]
Enicostemma axillare	-	Ethyl actetate	Carbon tetrachloride	[73]
Erycibe expansa	Stem	Methanol	D-galactosamine	[74]
Feronia limonia	Root	Methanol	Carbon tetrachloride	][75]
Ficus carica	Leaves	Methanol	Carbon tetrachloride	[76]
Ficus chlamydocarpa	-	Methanol	Carbon tetrachloride	[77]
Flacourtia indica	Aerial parts	Petroleum ether and Ethyl acetate	Paracetomol	[78]
Flaveria trinervia	Leaves	Methanol	Carbon tetrachloride	[79]
Enicostemma littorale	Whole plant	Alcohol	Carbon tetrachloride	[80]
Gentiana scabra	-	Aqueous	Carbon tetrachloride	[81]
Gundelia tourenfortii	Stalk	Hydro-alcoholic	Carbon tetrachloride	[82]
Hygrophila auriculata	Seeds	Methanol	Paracetomol + Thioacetamide	[83]
Hypoestes triflora	Leaves	Aqueous	Carbon tetrachloride	[84]
Indian Phyllanthus	Leaves and Stem	Methanol	tert-Butyl Hydroperoxide (t-BH) induced	[85]
Kalanchoe pinnata	Leaves	Ethanol	Carbon tetrachloride	[86]
Luffa echinata	Fruit	Petroleum ether, Acetone, Methanol	Carbon tetrachloride	[87]
Ocimum basilicum	Leaves	Ethanol	Carbon tetrachloride + Hydrogen peroxide	[88]
Lagenaria breviflora	Fruit	Ethanol	Carbon tetrachloride	[89]
Lepidium sativum	-	Methanol	Carbon tetrachloride	[90]
Luffa acutangula	-	Hydro-alcoholic	Carbon tetrachloride + Rifampicin	[91]
Meconopsis integrifolia	Whole part	Ethanol	Carbon tetrachloride	[92]
Melochia corchorifolia	Aerial parts	Ethanol/ethyl acetate/hexane	Carbon tetrachloride	[93]
monochoria vaginalis	Whole parts	Methanol	Carbon tetrachloride	[94]
Moraceae Ficus carica	Leaves	Methanol	Carbon tetrachloride	[95]
Morinda citrifolia	-	-	Carbon tetrachloride	[96]
Moringa oleifera	Leaves	Hydro-ethanolic	Paracetomol	[99]
Nymphaea stellata	Flowers	Alcohol	Carbon tetrachloride	[100]
Orthosiphon stamineus	Leaves	Methanol	Paracetomol	[101]
Phyllanthus atropurpureus	Aerial parts	Alcoholic	Carbon tetrachloride	[102]
Phyllanthus maderaspatensis	Whole plant	n-Hexane	Carbon tetrachloride + Thioacetamide	[103]
Phyllanthus niruri	Leaves	Aqueous	Paracetomol	[104]
Prostechea michuacana	-	Methanol	Carbon tetrachloride and Paracetomol	[105]
Pterocarpus marsupium	Bark	Methanol	Carbon tetrachloride	[106]
Rhinacanthus nasuta	Root	Methanol	Carbon tetrachloride	[107]
Sargassum polycystum	-	Ethanol	D-galactosamine	[108]
Silybum marianum	-	Polyphenolic extracts	Thioacetamide	[109]
smilax perfoliata	Aerial parts	Ethanol	Carbon tetrachloride	[110]
Solanum elaeagnifolium		Aqueous-methanolic	Acetaminophen	[111]
Solanum nigrum	-	Aqueous	Carbon tetrachloride	[112]
Solanum xanthocarpum	Fruits	Ethanol	Carbon tetrachloride	[113]
Sarcostemma brevistigma	Bark	Ethyl acetate	Carbon tetrachloride	[114]
Thonningia sanguinea	Roots, Leaves	Aqueous	Carbon tetrachloride and d- galactosamine	[115]
Trianthema portulacastrum	Leaves	Ethanol	Paracetomol + Thioacetamide	[116]
Terminalia belerica	Fruits	Ethanol	Carbon tetrachloride	[117]
Terminalia arjuna	Leaves	Aqueous	Tertiary Butyl Hydroperoxide	[118]
Trigonella foenum-graecum	Leaves	Ethanol	Carbon tetrachloride + Hydrogen peroxide	[119]
Vitis thunbergii	Leaves	Ethanol	Carbon tetrachloride	[120]
Wedelia calendulacea	Leaves	Ethanol	Carbon tetrachloride	[121]

Modern pharmaceuticals still contain at least 25% drugs derived from natural sources. Medicinal plants have various pharmacological properties against wide range of chronic disorders on living systems. The use of natural remedies for the treatment of liver diseases has a long history and medicinal plants and their bioactive principles are still used

all over the world in one form or another for this biomedical purpose. Liver protective medicinal plants contain a variety of chemical bioactive constituents like phenols, coumarins, monoterpenes, glycosides, alkaloids and xanthenes [23-24]. In this review manuscript, we review the literature related to natural products (crude plant extracts and chemically defined molecules) with hepatoprotective activity against hepatotoxin induced liver toxicity (Table. 1). These findings provide greater chances and flexibility in helping biomedical researchers to identify the effective hepato-protective plants further pre-clinical studies and to establish the clear experimental model to conduct further studies.

CONCLUSION

Liver diseases continue as one of the foremost health problems worldwide including developing and developed countries, with liver cirrhosis and drug induced liver injury accounting ninth leading cause of death particularly in western and throughout the world. Currently available treatments synthesized along the principles of western medicine are often limited in efficacy, and also produce unwanted side effects to human health. Another major drawback of this medicine, are often too costly, especially for the developing countries. Therefore, treating liver diseases with plant-derived natural bioactive compounds which are easily accessible to everyone and do not require laborious pharmaceutical synthesis seems highly attractive. In this review article, our major objective was to compile the reported hepatoprotective medicinal plants from worldwide against toxic chemicals that cause liver injury and may be useful to the health professionals, biomedical scientists and research scholars working the field of pharmacology and therapeutics to develop evidence-based alternative medicine to cure different kinds of liver diseases/disorders in man and animals. Moreover, further investigation including clinical trials need to be conduct to confirm the safety of these bioactive natural compounds as a good alternative drugs without any toxicity to conventional drugs in the treatment of liver diseases.

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