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Full Length Research Paper

A review of natural products with hepatoprotective activity

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Liver diseases are a major worldwide health problem, with high endemicity in developing countries. They are mainly caused by chemicals and some drugs when taken in very high doses. Despite advances in modern medicine, there is no effective drug available that stimulates liver function, offer protection to the liver from damage or help to regenerate hepatic cells. There is urgent need, therefore, for effective drugs to replace/supplement those in current use. The plant kingdom is undoubtedly valuable as a source of new medicinal agents. The present work constitutes a review of the literature on plant extracts and chemically defined molecules of natural origin with hepatoprotective activity. The review shows 107 plants, their families, geographical distribution, plant parts utilized, type of assay and inducer of liver damage. It also includes 58 compounds isolated from higher plants, classified into appropriate chemical groups. This work intends to aid researchers in the study of natural products useful in the treatment of liver diseases.

Key words: Liver, liver disease, hepatoprotective activity, natural products.

INTRODUCTION

The liver is the most important organ in the body. It plays a pivotal role in regulating various physiological processes. It is also involved in several vital functions, such as metabolism, secretion and storage. It has great capacity to detoxicate toxic substances and synthesize useful principles (Shanani, 1999; Subramoniam and Pushpangadan, 1999). It helps in the maintenance, performance and regulating homeostasis of the body. It is involved with almost all the biochemical pathways to growth, fight against disease, nutrient supply, energy provision and reproduction. In addition, it aids metabolism of carbohydrate, protein and fat, detoxification, secretion of bile and storage of vitamins (Ahsan et al., 2009). 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 (Bodakhe and Ram, 2007).

Liver diseases remain one of the major threats to public health and are a worldwide problem (Asha and Pushpangadan, 1998). They are mainly caused by chemicals like acetaminophen (in large doses), excess consumption of alcohol, infections and autoimmune disorders. Most of the hepatotoxic chemicals damage liver cells mainly by inducing lipid peroxidation and other oxidative damages (Recknagel, 1983; Wendel et al., 1987; Dianzani et al., 1991). Acetaminophen, a mild analgesic and antipyretic drug, developed in the last century, causes serious liver necrosis in humans and in experimental animals if taken in large doses (Lin et al., 1995; Mitchell et al., 1973; Hinson 1980 and Mitchell, 1988). While alcohol is one of the main causes of end-stage liver disease worldwide, alcoholic liver disease is the second most common reason for liver transplantation in the United States (Mandayam et al., 2004). Due to increased frequency of drinking and change of diet construction, such as the increase of fat content, the incidence of liver diseases has increased in China, becoming another important risk factor for morbidity and mortality in addition to viral hepatitis (Zhuang and Zhang, 2003). The spectrum of alcoholic liver disease ranges from fatty liver to alcoholic hepatitis and ultimately fibrosis and cirrhosis (Tuma and Sorrell, 2004).

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In spite of the tremendous advances in modern medicine, there is no effective drug available that stimulates liver function, offer protection to the liver from damage or help to regenerate hepatic cells (Chattopadhyay, 2003). It is therefore necessary to search for alternative drugs for the treatment of liver diseases to replace currently used drugs of doubtful efficacy and safety.

Medicinal plants play a key role in human health care. About 80% of the world population relies on the use of traditional medicine, which is predominantly based on plant material (WHO, 1993). Scientific studies available on medicinal plants indicate that promising phytochemicals can be developed for many health problems (Gupta, 1994). For example, the vinca alkaloids (vincristine, vinblastine and vindesine), derived from *Catharanthus roseus*, *Vinca rosea*, *Lochnera rosea*, and *Ammocallis rosea* have been employed for their anti-cancer properties. Modern pharmaceuticals still contain at least 25% drugs derived from plants. Medicinal plants have various effects on living systems. Some are sedatives, analgesics, antipyretics, cardioprotectives, antibacterial, antiviral and antiprotozoal (Olaleye et al., 2006). 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 another for this purpose. Liver protective plants contain a variety of chemical constituents like phenols, coumarins, monoterpenes, glycosides, alkaloids and xanthenes (Bhawna and Kumar, 2009). In this work, we review the literature related to natural products (crude plant extracts and chemically defined molecules) with hepatoprotective activity. These findings provide greater chances and flexibility in helping researchers identify compounds with good hepatoprotective potential.

METHODOLOGY

For the present review, we conducted a literature search (up to October 2009), using Elsevier-Science direct, SpringerLink (Springer/Kluwer), Wiley Interscience (Wiley), Pubmed and Google Scholar. The search included the following keywords: “plants”, “medicinal plants”, “plant extracts”, cross-referenced with the keywords: “hepatoprotective”, “liver diseases”, “hepatoprotective activity”. The references found in the search were later consulted for details on the models or bio-assays used for testing the plant extracts against liver diseases.

Hepatoprotective activity of crude plant extracts

The aetiology of liver diseases is diverse and a variety of plants has been reported to show hepatoprotective activity and so may be useful in the treatment of these diseases. A list of plants reported to have significant hepatoprotective activity is shown in Table 1 in alphabetical order of their family, together with their scientific names, origin, plant part used, kind of extract used, type of assay and inducer of liver damage.

Apium graveolens L. grows wild at the base of the North Western Himalayas and outlying hills in Punjab and in Western India. The seeds are used in India to treat bronchitis, asthma, liver and spleen diseases. Its hepatoprotective effect was tested against paracetamol and thioacetamide induced liver injury in rats. The results obtained after oral administration of the methanolic extract of the seeds of *A. graveolens* suggest that this plant has hepatoprotective action which may be due to its role as a membrane stabilizer (Singh and Handa, 1995).

Suja et al. (2004) reported the effect of the methanol extract of *Helminthostachys zeylanica* (L.)Hook rhizomes on carbon tetrachloride (CCl_4) induced liver damage in wistar rats. The results showed that significant hepatoprotective effect was obtained against CCl_4 induced liver damage, by oral administration of *H. zeylanica* methanol extract as evident from decreased levels of serum enzymes and an almost normal architecture of the liver, in the treated groups, compared to the controls. Thus, the study provides a scientific rationale for the traditional use of this plant in the management of liver diseases.

The hepatoprotective activity of the leaf extract of *Alchornea cordifolia* (Schum and Thonn), a Nigerian plant on acetaminophen induced toxicity *in vivo* has been reported (Olaleye et al., 2006). The antioxidative properties revealed total phenolic content of 0.22 mg/ml and reducing power of 0.062 mg/ml as compared to vitamin E with a reducing power of 0.042 mg/ml. The authors concluded that the hepatoprotective activity of this plant on acetaminophen-induced liver damage is connected to its antioxidative properties.

Dahiru et al. (2005) reported the protective effect of the ethanol extract of the leaves of *Ziziphus mauritiana* Lam., on CCl_4 induced liver damage. Pretreatment of rats with 200 and 300 mg/kg body weight of *Z. mauritiana* leaf extract protected rats against CCl_4 liver injury by significantly lowering aspartate aminotransaminase, alanine aminotransaminase, alkaline phosphatase, total bilirubin, and lipid peroxide levels compared to control.

The fruit pulp of *Adansonia digitata* (Linn.), commonly known as baobab is an important human nutrition source in East, Central and West Africa (Beckier, 1983; Szolnoki, 1985). The aqueous extract of *A. digitata* pulp was tested for hepatoprotective activity against liver injury by CCl_4 in rats. The aqueous extract exhibited significant hepatoprotective activity and consumption of the fruit may play an important part in human resistance to liver damage in areas where the plant is consumed (Didibe et al., 1996). The mechanism of liver protection may be due to the presence of triterpenoids, β-sitosterol, β-amyrin palmitate and ursolic acid in the fruit pulp of *A. digitata* (Al-Qarawi et al., 2003).

Bishayee et al. (1995) reported the hepatoprotective effect of aqueous extracts of fresh tuber roots of *Daucos carota* L. on CCl_4-induced acute liver damage. The increased serum enzyme levels by CCl_4 induction were lowered due to pretreatment with the extract. The extract also decreased the elevated serum bilirubin and urea content due to CCl_4 administration. Results of this study revealed that *Daucos carota* could afford a significant protective action in the alleviation of CCl_4 induced hepatocellular injury.

Cassia occidentalis L. a weed of the family Caesalpinaceae is found throughout India and is an important ingredient of several polyherbal formulations marketed for liver diseases. The hepatoprotective activity of aqueous-ethanolic extract (50%, v/v) of leaves was studied on rat liver damage induced by paracetamol and ethyl alcohol by monitoring serum transaminase, alkaline phosphatase, serum cholesterol, serum total lipids and histological alterations. The leaf extract was shown to possess significant hepatoprotective property (Jafri et al., 1999).

Rhoicissus tridentata (L.F) Wild and Drum, a South African medicinal plant is commonly used for the treatment of ailments like epilepsy, kidney and bladder complaints (Opoku et al., 2007). The aqueous extract of the roots were shown to possess significant hepatoprotective effect against CCl_4 induced acute liver injury in rats. The variables investigated were the enzymes alanine aminotransferase, aspartate aminotransferase and glucose-6-phospate (G-6-Pase). CCl_4 intoxication resulted in significant

Table 1. Plant extracts with hepatoprotective activity.

Family and botanical name	Origin	Part used	Extract	Type of assay and inducer of liver damage	References
Acanthaceae					
Acanthus ilicifolius L.	India	Leaves	Alcohol	*In vivo*; CCl_4	Babu et al. (2001)
Andrographis lineata Nees	India	Leaves	Aqueous, methanol	*In vivo*; CCl_4	Sangameswaran et al. (2008)
Andrographis paniculata (Burm.f.) Nees	India	Leaves	Alcohol	*In vivo*; CCl_4	Rana and Avadhoot (1991)
Anisotes trisulcus (Forssk.)	Yemen	a	Ethanol	*In vivo*; CCl_4	Fleurentin et al. (1986)
Asteracantha longifolia L.	Sri Lanka	Whole plant	Aqueous	*In vivo*; CCl_4 and PCM	Hewawasam et al. (2003)
Hygrophila auriculata (K.Schum.) Heine	India	Seeds	Methanol	*In vivo*; PCM and thioacetamide	Singh and Handa (1995)
Hypoestes triflora (Forssk.) Roem. and Schult	Rwanda	Leaves	Aqueous	*In vivo*; CCl_4	Van Puyvelde et al. (1989)
Rhinacanthus nasuta (L.) Kurz.	India	Root	Methanol	*In vivo*; CCl_4	Suja et al. (2003)
Adoxaceae *Viburnum tinus* L.	Southern Europe	Leaves	Aqueous-methanol	*In vivo*; CCl_4	Mohammed et al. (2005)
Aizoaceae *Trianthema portulacastrum* L.	India	Leaves	Ethanol	*In vivo*; PCM and thioacetamide	Kumar et al. (2004)
Apiaceae *Apium graveolens* L.	India	Seeds	Methanol	*In vivo*; PCM and thioacetamide	Singh and Handa (1995)
Carum copticum L.	Pakistan	Seeds	Aqueous- methanol	*In vivo*; CCl_4 and PCM	Gilani et al. (2005a)
Apocynaceae *Apocynum venetum* L.	China, Japan	Leaf	Aqueous	*In vivo*; CCl_4 and GAIN	Xiong et al. (2000)
Araliaceae *Acanthopanax senticosus* (Rupr. and Maxim.) Harms	Taiwan	a	a	*In vivo*; CCl_4 and acetaminophen	Lin and Huang (2002)

Table 1. Contd.

Asclepiadaceae *Sarcostemma brevistigma* Wight	India	Stem bark	Ethyl acetate	*In vivo*; CCl_4	Sethuraman et al. (2003)
Asteraceae *Achyrocline satureioides* (Lam.) DC.	Argentina	Aerial parts	Aqueous	*In vivo*; Bromobenzene	Kadarian et al. (2002)
Artemisia absinthium L.	Pakistan	Aerial parts	Aqueous-methanol	*In vivo*; CCl_4 and acetaminophen	Gilani and Janbaz (1995a)
Artemisia maritima L	Pakistan	Aerial parts	Aqueous-methanol	*In vivo*; CCl_4 and acetaminophen	Janbaz and Gilani (1995)
Artemisia vulgaris L.	Pakistan	Aerial parts	Aqueous-methanol	*In vivo*; GAIN and LPS	Gilani et al. (2005b)
Bidens chilensis DC	Taiwan	a	a	*In vivo*; CCl_4 and PCM	Chih et al. (1996)
Bidens pilosa L.	Taiwan	a	a	*In vivo*; CCl_4 and PCM	Chih et al. (1996)
Cichorium intybus L.	India	Seeds	Alcohol	*In vivo*; CCl_4	Ahmed et al. (2003)
Crassocephalum crepidioides Benth	Japan	Whole plant	Aqueous	*In vivo* and *in vitro*; GAIN, LPS and CCl_4	Aniya et al. (2005)
Elephantopus mollis Kunth.	Taiwan	Whole plant	Aqueous	*In vivo*; acetaminophen and GAIN	Lin et al.(1995b)
Elephantopus scaber L.	Taiwan	Whole plant	Aqueous	*In vivo*; acetaminophen and GAIN	Lin et al. (1995b)
Flaveria trinervia (Spreng.) C.Mohr	India	Leaf	Methanol	*In vivo*; CCl_4	Umadevi et al. (2004)
Gundelia tourenfortii L.	Iran	Stalk	Hydro-alcoholic	*In vivo* and *in vitro*; CCl_4	Jamshidzadeh et al. (2005)
Pseudoelephantopus spicatus (Juss. Ex Aublet) Gleason	Taiwan	Whole plant	Aqueous	*In vivo*; acetaminophen and GAIN	Lin et al. (1995b)
Wedelia chinensis (Osbeck) Merr.	Taiwan	a	a	*In vivo*; CCl_4, acetaminophen and GAIN	Lin et al. (1994)
Wedelia calendulacea L.	India	Leaf	Ethanol	*In vivo*; CCl_4	Murugaian et al. (2008)

Table 1. Contd.

Balanophoraceae *Thonningia sanguinea* Vahl.	Ghana	Roots, leaves	Aqueous	*In vivo* and in vitro; GAIN and CCl_4	Gyamfi et al. (1999)
Bixaceae *Cochlospermum tinctorium* Perri ex Rich.	Mali	Rhizome	Ethanol and hydro-ethanol extract	*In vivo*; CCl_4	Diallo et al. (1992)
Bixa orellana L.	Bangladesh	Seed	Methanol	*In vivo*; CCl_4	Ahsan et al. (2009)
Brassicaceae *Coronopus didymus* L.	India	Whole plant	Aqueous	*In vivo*; CCl_4	Mantena et al. (2005)
Burseraceae *Commiphora opobalsamum* (L.) Engl.	Saudi Arabia	Aerial parts	Ethanol	*In vivo*; CCl_4	Al-Howiriny et al. (2004)
Caesalpiniaceae *Bauhinia racemosa* Lam.	India	Bark	Methanol	*In vivo*; CCl_4 and PCM	Gupta et al. (2004)
Capparidaceae *Cleome viscosa* L	India	Leaves	Ethanol	*In vivo*; CCl_4	Gupta et al. (2009)
Casuarinaceae *Casuarina equisetifolia* Forst	Bangladesh	Leaves, bark	Methanol	*In vivo*; CCl_4	Ahsan et al. (2009)
Celasteraceae *Salacia reticulata* Wight	Sri Lanka, India	Root, stem	Aqueous, methanol	*In vivo*; CCl_4	Yoshikawa et al. (2002)
Chenopodiaceae *Beta vulgaris* L.	India	Root	Ethanol	*In vivo*; CCl_4	Agarwal et al. (2006)
Combretaceae *Combretum* Kurz.	Japan	Leaves	Methanol	*In vivo* and *in vitro*, GAIN	Banskota et al. (2003)
Terminalia arjuna L.	India	Bark	Aqueous	*In vivo*; CCl_4	Manna et al. (2006)
Terminalia belerica Roxb	India	Fruits	Ethanol	*In vivo*; CCl_4	Jadon et al. (2007)
Terminalia catappa L.	Okinawa Island	Leaves	Aqueous	*In vivo* and *in vitro*; GAIN and LPS	Kinoshita et al. (2007)
Terminalia chebula Reiz.	India	Fruits	Ethanol	*In vivo* and *in vitro*; Anti TB drugs	Tasduq et al. (2006)

Table 1. Contd.

Compositae *Ambrosia maritima* L.	Egypt	Whole plant	Aqueous-methanol	*In vivo*; acetaminophen	Ahmed and Kharter (2001)
Crepis rueppellii (Sch.) Bip.	Yemen	a	Ethanol	*In vivo*; CCl_4	Fleurentin et al. (1986)
Eclipta alba Hassk.	India	a	Alcohol	*In vivo*; CCl_4	Singh et al. (1993)
Epaltes divaricata (L.) Cav.	India	Whole plant	Aqueous	*In vivo*; CCl_4	Hewawasam et al. (2004)
Convolvulaceae *Cuscutae semen* Lam.	Korea	Seeds	Aqueous	*In vivo*; DMN	Kim et al. (2007a)
Erycibe expansa Wall. and G.Don	Thailand	Stem	Methanol	*In vitro*; GAIN	Matsuda et al. (2004)
Crassulaceae *Kalanchoe pinnata* Pers.	India	Leaves	Juice of leaves, ethanol extract of marc	*In vivo* and *in vitro*; CCl_4	Yadav and Dixit (2003)
Cucurbitaceae *Luffa echinata* Roxb.	India	Fruits	Pet. ether, acetone, methanol	*In vivo*; CCl_4	Ahmed et al. (2002)
Cyperaceae *Cyperos scariosus* R.Br.	Indonesia, Pakistan	Tubers	Aqueous-methanol	*In vivo*; CCl_4	Gilani and Jambaz (1995b)
Ebenaceae *Diospyros malabarica* (Desr.) Kostel	India	Bark	Methanol	*In vivo*; CCl_4	Mondal et al. (2005)
Euphorbiaceae *Alchornea cordifolia* Schum and Thonn.	Nigeria	Leaves	Ethanol	*In vivo*; acetaminophen	Olaleye et al. (2006)
Croton oblongifolius Roxb.	India	Aerial parts	Pet. ether, acetone, methanol	*In vivo*; CCl_4	Ahmed et al. (2002)
Emblica officinalis Gaertner	India	Fruits	Hydro-alcoholic	*In vitro*; Anti TB drugs	Tasduq et al. (2005)
Phyllanthus maderaspatensis L.	India	Whole plant	n-hexane	*In vivo*; CCl_4 and thioacetamide	Asha et al. (2007)

Table 1. Contd.

Phyllanthus niruri L.	Brazil	Leaves	Aqueous	*In vivo*; PCM	Sabir and Rocha (2008)
Phyllanthus polyphyllus L.	a	a	Methanol	*In vivo*; PCM	BR et al. (2008)
Phyllanthus reticulatus Poir.	a	Aerial parts	Ethanol	In vivo; CCl_4	Das et al. (2008)
Fabaceae *Acacia catechu* (L.f.) Willd.	India	Bark	Ethyl acetate	*In vivo*; CCl_4	Ray et al. (2006)
Bauhinia variegata L.	India	Stem bark	Alcohol	*In vivo*; CCl_4	Bodakhe and Ram (2007)
Cajanus cajan L.	India	Leaves	Methanol	*In vivo*; alcohol	Kundu et al.(2008)
Cassia fistula L.	India	Leaves	n-heptane	*In vivo*; CCl_4	Bhakta et al. (1999)
Cassia occidentalis L.	India	Leaves	Aqueous-ethanol	*In vivo*; PCM and ethyl alcohol	Jafri et al. (1999)
Glycine max (L.) Merr	Taiwan	Seed	Water	*In vivo*; acetaminophen	Wu et al. (2001)
Phaseolus aureus Roxb.	Taiwan	Seed	Water	*In vivo*; acetaminophen	Wu et al. (2001)
Phaseolus calcaratus Roxb	Taiwan	Seed	Water	*In vivo*; acetaminophen	Wu et al. (2001)
Phaseolus radiatus L.	Taiwan	Seed	Water	*In vivo*; acetaminophen	Wu et al. (2001)
Pterocarpus marsupium Roxb.	India	Stem bark	Methanol	*In vivo*; CCl_4	Mankani et al. (2005)
Trigonella foenum-graecum L.	a	Leaves	Ethanol	H_2O_2; CCl_4	Meera (2009)
Fumariaceae *Fumaria indica* (Hausskn.) Pugsley	India	Whole plant	Methanol, Pet. Ether, aqueous	*In vivo*; PCM, Rifampicin, CCl_4	Rao and Mishra (1997)
Fumaria parviflora Lam.	Pakistan	Shoots	Aqueous-methanol	*In vivo*; PCM	Gilani et al. (1996)
Gentianaceae *Enicostemma littorale* Blume.	India	Whole plant	Alcohol	*In vivo*; CCl_4	Senthilkumar et al. (2005)
Swertia japonica (Roem. and Schult.) Makino.	Japan	Whole plant	Butanol	*In vivo*; GAIN	Hase et al. (1997b)
Lamiaceae *Ocimum basilicum* L.	a	Leaves	Ethanol	H_2O_2; CCl_4	Meera et al. (2009)

Table 1. Contd.

Moraceae *Ficus carica* L.	India	Leaves	Methanol	*In vivo*; CCl_4	Krishna et al. (2007)
Ficus hispida L	India	Leaves	Methanol	*In vivo*; PCM	Mandal et al. (2000)
Moringaceae *Moringa oleifera* L.	Malaysia	Leaves	Hydro-alcoholic	*In vivo*; acetaminophen	Fakurazi et al. (2008)
Myrtaceae *Careya arborea* Roxb.	India	Stem bark	Methanol	*In vivo*; CCl_4	Sambath et al. (2005)
Nyctaginaceae *Boerhaavia diffusa* L.	India	Roots	Aqueous	*In vivo*; thioacetamide	Rawat et al. (1997)
Nymphaceae *Nymphaea stellata* Willd.	India	Flowers	Alcohol	*In vivo*; CCl_4	Bhandarkar and Khan (2004)
Oleaceae *Phillyrea latifolia* L.	Jordan	Leaves	Aqueous	*In vivo*; CCl_4	Janakat and Al-Merie (2002)
Ophioglossaceae *Helminthostachys zeylanica* (L.) Hook	India	Rhizomes	Methanol	*In vivo*; CCl_4	Suja et al. (2004)
Orchidaceae *Anoectochilus formosanus* Hayata	Taiwan	Whole plant	Aqueous	*In vivo* and *in vitro*; CCl_4	Wu et al. (2007)
Polygalaceae *Polygala arvensis* Willd.	India	Leaves	Chloroform	*In vivo*; GAIN	Dhanabal et al. (2006)
Rhamnaceae *Ventilago leiocarpa* Benth.	Taiwan	Bark	Methanol, ethanol, butanol and aqueous	*In vivo*; CCl_4	Lin et al. (1995a)
Ziziphus mauritiana Lam.	Nigeria	Leaves	Ethanol	*In vivo*; CCl_4	Dahiru et al. (2005)
Rubiaceae *Hedyotis corymbosa* (L.) Lam.	India	Whole plant	Methanol	*In vivo*; PCM	Sadasivan et al. (2006)
Mitracarpus scaber Zucc.	Mali	a	a	*In vivo* and *in vitro*; Cl_4	Germano et al. (1999)
Morinda citrifolia L.	America	a	a	*In vivo*; CCl_4	Wang et al. (2008)

Table 1. Contd.

Rutaceae *Aegle marmelos* (L.) Corr. Serr.	India	Leaves	Fine powder in physiological saline	*In vivo*; alcohol	Singanan et al. (2007)
Glycosmis pentaphylla Corr.	Bangladesh	Leaves, bark	Methanol	*In vivo*; CCl_4	Ahsan et al. (2009)
Scrophulariaceae *Bacopa monniera* (L.) Pennell	India	a	Alcohol	*In vivo*; morphine	Sumathy et al. (2001)
Picrorrhiza kurroa (Roule.) Sans	Himalayas	Rhizome, roots	Ethanol	*In vivo*; GAIN	Anandan and Devaki (1999)
Smilacaceae *Smilax regelii* Killip and Morton	Saudi Arabia	Roots	Ethanol	*In vivo*; CCl_4	Rafatullah et al. (1991)
Solanaceae *Nicotiana glauca* Graham.	Jordan	Leaves, flowers	Aqueous	*In vivo*; CCl_4	Janakat and Al-Merie (2002)
Solanum nigrum L	India	Fruits	Ethanol	*In vivo*; CCl_4	Raju et al. (2003)
Solanum pseudocapsicum Hassl.	Jerusalem	Leaves	Methanol	*In vivo* and *in vitro*; CCl_4	Vijayan et al. (2003)
Solanum trilobatum L.	India	Whole plant	Methanol	*In vivo*; CCl_4	Shahjahan et al. (2004)
Umbelliferae *Bupleurum kaoi* Liu (Chao et Chuang)	Taiwan	Leaves	Aqueous	*In vitro*; acetaminophen and CCl_4	Liu et al. (2006)
Daucus carota L.	Europe, Asia, Africa	Roots	Aqueous	*In vivo*; CCl_4	Bishayee et al. (1995)
Foeniculum vulgare Miller	Turkey	Seeds	Essential oil	*In vivo*; CCl_4	Ozbek et al. (2003)
Valerianaceae *Nardostachys jatamansi* D.C.	India	Rhizomes	Ethanol	*In vivo*; CCl_4	Ali et al. (2000)
Vitaceae *Rhoicissus tridentata* (L.f.) Wild and R.B. Drumm	South Africa	Roots	Aqueous	*In vivo*; CCl_4	Opoku et al. (2007)

a, Data incomplete (derived from an abstract); CCl_4, carbon tetrachloride; PCM, paracetamol; GAIN, d-galactosamine; LPS, lipopolysaccharide; TB, tuberculosis; DMN, dimethynitrosamine; Pet. ether, petroleum ether.

increases in all the variables investigated except G-6-Pase which was significantly decreased. The administration of *R. tridentata* extracts after CCl_4 intoxication resulted in significant decreases in all the variables investigated except G-6-Pase which was significantly increased (Opoku et al., 2007).

In a recent study by Ahsan et al. (2009), the methanol extracts of *Bixa orellana*, *Cajanus cajan*, *Glycosmis pentaphylla* and *Casuarina equisetifolia* were all shown to possess significant hepatoprotective activity. The four plant extracts at a dose of 500 mg/kg body weight exhibited moderate protective effect by lowering the serum levels of alanine aminotransferase (ALT) or serum glutamate pyruvate transaminase (SGPT), aspartate aminotrans-ferase (AST) or serum glutamate oxaloacetate transaminse (SGOT), and cholesterol to a significant extent against liver damage induced by CCl_4. It was possible to list 107 species of medicinal plants studied, that have shown hepatoprotective activity.

These species are distributed in 47 families, of which the following stood out: Asteraceae, Fabaceae and Acanthaceae with 15, 11 and 8 species, respectively.

It is easy to perceive the potential in these plants as attractive targets for future studies, to identify the active constituents and possibly to uncover new alternatives to the existing therapies for liver diseases. Such future studies will be necessary to expand the existing, limited therapeutic arsenal for the majority of liver diseases, especially for those therapies with side effects that limit their effectiveness.

Chemically defined molecules with hepatoprotective activity

Several chemically defined molecules have been isolated from crude plant extracts with proven hepatoprotective activity. A list of these compounds is shown in Table 2 with information on the chemical name and class of the compounds.

New skeletal flavonoids, anastatins A and B, were isolated from the methanol extract of *Anastatica hierochuntica* L. Anastatins A and B were found to show hepatoprotective effects on D-galactosamine-induced cytotoxicity in primary cultured mouse hepatocytes and their activities were stronger than those of related flavonoids and commercial silybin - a known hepatoprotective compound (Yoshikawa et al., 2003).

Farombi (2000) examined the protective mechanisms of kolaviron, a biflavonoid fraction from *Garcinia kola* (Heckel) seeds in rats treated with CCl_4. When administered at a dose of 1.2 g kg^{-1}, three times a week for two weeks, it significantly depressed the activities of microsomal aniline hydroxylase, aminopyrine N-demethylase, ethoxyresorufin O-demethylase and p-nitroanisole O-demethylase. Kolaviron (200 mg kg^{-1}), administered for 14 days consecutively, inhibited the CCl_4 mediated decrease in the activities of these enzymes by 60, 65, 55 and 63% respectively. Kolaviron exerted its protective action by acting as an *in vivo* natural antioxidant and by enhancement of drug-detoxifying enzymes.

Picroliv, an iridoid glycoside isolated from *Picrorhiza kurrooa* (Royle ex Benth) demonstrated dose-dependent protective activity on isolated hepatocytes against paracetamol-induced hepatic damage in rats. It also restored the normal values of enzymes (glutamic oxaloacetic transaminase, glutamic-pyruvic transaminase, and alkaline phosphatase) both in the isolated hepatocyte suspension as well as in the serum (Visen et al., 1991).

Hepatoprotective activity-guided fractionation of the methanol extract of *Equisetum arvense* L. resulted in the isolation of two phenolic petrosins and four flavonoids. Among these compounds, onitin and luteolin demonstrated hepatoprotective activities on tacrine-induced cytotoxicity in human liver-derived Hep G2 cells, displaying EC (50) values of 85.8 +/- 9.3 microM and 20.2 +/- 1.4 microM, respectively. Silybin used as a positive control, showed the EC (50) value of 69.0 +/- 3.3 microM. Both compounds also showed superoxide scavenging effects which indicates good antioxidant activity. These results support the use of *E. arvense* in the treatment of hepatitis in oriental traditional medicine (Oh et al., 2004).

Two triterpenes α- and β-amyrin isolated from *Protium heptaphyllum* (Aubl.) March. were tested against acetaminophen-induced liver injury in mice. Liver injury was analysed by quantifying the serum enzyme activities and by histopathological observation. Pretreatment with α- and β-amyrin attenuated the acetaminophen-induced acute increase in serum alanine aminotransferase and aspartate aminotransferase activities, replenished the depleted hepatic glutathione, and considerably reduced the histopathological alterations. These findings demonstrated the hepatoprotective potential of α- and β-amyrin against toxic liver injury and suggest that the diminution in oxidative stress and toxic metabolite formation as likely mechanisms involved in its hepatoprotection (Oliveira et al., 2005).

We encountered 58 chemically defined natural molecules reported in the literature, which have been evaluated for hepatoprotective activity. These compounds can serve as important leads, for the discovery of new drugs in the treatment of liver diseases. However, for many of these compounds, the clinical data are very limited. Clinical efficacy and potential toxicity of active compounds in larger trials requires further assessment, before recommendations concerning their routine use can be identified.

Conclusion

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. 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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REFERENCES

Adnyana K, Tezuka Y, Awale S, Banskota AH, Kim QT, Kadota S (2001). 1-0-galloyl-6- 0-(4-hydroxy-3, 5-dimethoxy) benzoyl-β-d-glucose, a new hepatoprotective constituent from *Combretum*

Table 2. Chemically defined molecules with hepatoprotective activity.

Chemical substance	Plant	Plant part	Class	References
3,4-di-O-caffeoylquinic acid	*Lactuca indica* L.	Aerial parts	Quinic acid	Kim et al. (2007b)
3,5-di-O-caffeoyl-muco-quinic acid	*Lactuca indica* L.	Aerial parts	Quinic acid	Kim et al. (2007b)
5-O-(E)-p-coumaroylquinic acid	*Lactuca indica* L.	Aerial parts	Quinic acid	Kim et al. (2007b)
α-Amyrin	*Protium heptaphyllum* (Aubl.) March	Trunk wood resin	Triterpene	Oliveira et al. (2005)
β-Amyrin	*Protium heptaphyllum* (Aubl.) March	Trunk wood resin	Triterpene	Oliveira et al. (2005)
Anastatin A	*Anastatica hierochuntica* L.	Whole plant	Flavonoid	Yoshikawa et al. (2003)
Anastatin B	*Anastatica hierochuntica* L.	Whole plant	Flavonoid	Yoshikawa et al. (2003)
18β-glycyrrhetinic acid	*Glycyrrhiza uralensis* Fisch.	Rhizomes	Glycyrrhetinic acid	Shim et al. (2000)
Tetrahydroswertianolin	*Swertia japonica* Makino	a	Xanthione	Hase et al. (1997b)
Gentiopicroside	*Swertia japonica* Makino	a	Iridoid	Hase et al. (1997b)
Sweroside	*Swertia japonica* Makino	a	Iridoid	Hase et al. (1997b)
Andrographolide	*Andrographis paniculata* (Burm.f)Nees	a	Diterpene	Chander et al. (1995)
Erycibenin A	*Erycibe expansa* Wall. Ex G.Don.	Stem	Pterocarpane	Matsuda et al. (2004)
5,7,4´-trihydroxy-3´-methoxyisoflavone	*Erycibe expansa* Wall. Ex G. Don.	Stem	Isoflavone	Matsuda et al. (2004)
Genistein	*Erycibe expansa* Wall. Ex G.Don.	Stem	Isoflavone	Matsuda et al. (2004)
Orobol	*Erycibe expansa* Wall. Ex G. Don.	Stem	Isoflavone	Matsuda et al. (2004)
Mangiferin	*Salacia reticulata* Abst.	Roots	Phenolic compound	Yoshikawa et al. (2002)
(-)-4´-O-methylepigallocatechin	*Salacia reticulata* Abst.	Roots	Phenolic compound	Yoshikawa et al. (2002)

Table 2. Cont'd

Thymoquinone	*Nigella sativa* L.	a	Quinone	Daba and Abdel-Rahman (1998)
Lithospermate B	*Salvia miltorhiza* Bunge	Roots	Caffeic acid	Hase et al. (1997a)
Taxiresinol	a	a	Tetrahydrofuran	Nguyen et al. (2004)
(7´R)-7´-hydroxylariciresinol	a	a	Tetrahydrofuran	Nguyen et al. (2004)
Onitin	*Equisetum arvense* L.	Aerial parts	Phenolic compound	Oh et al. (2004)
Luteolin	*Equisetum arvense* L.	Aerial parts	Flavonoid	Oh et al. (2004)
Quercetin-3-O-β-D-glucuronopyranoside	*Saururos chinensis* (Lour.) Baill.	a	Flavonol glycoside	Sung et al. (1997)
Quercetin-3-O-β-D-glucuronopyranosyl methyl ester	*Saururus chinensis* (Lour.) Baill.	a	Flavonol glycoside	Sung et al. (1997)
Scropolioside-A	*Scrophularia koelzii* Pennell	a	Iridoid glycoside	Garg et al. (1994)
3-(S)-3-β-D-glucopyranosyloxybutanolide	*Goodyera schlechtendaliana* Reichb. *G. matsumurana* Schltr. *G. discolor* Kergawl.	Whole plant	Aliphatic glycoside	Du et al. (2000)
3-(S)-3-β-D-glucopyranosyloxy-4-hydroxybutanoic acid	*Goodyera schlechtendaliana* Reichb. *G. matsumurana* Schltr. *G. discolor* Kergawl.	Whole plant	Aliphatic glycoside	Du et al. (2000)
Agathisflavone	*Canarium manii* King	a	Biflavonoid	Anand et al. (1992)
(S)-bakuchiol	*Psoralea corylifolia* Babchi	a	Monoterpene phenol	Hyun et al. (2001)
Monomethyl fumarate	*Fumaria indica* Pugsley	Whole plant	Fumaric acid	Rao and Mishra (1998)
Wighteone	*Cudrania cochinchinensis* (Lour.) Kudo et Masam.	Roots	Flavonoid	Lin et al. (1996)
Naringenin	*Cudrania cochinchinensis* (Lour.) Kudo et Masam.	Roots	Flavonoid	Lin et al. (1996)

Table 2. Cont'd

Torilin	*Cnidium monnieri* (L.) Cusson.	a	Sesquiterpene	Oh et al. (2002)
Torilolone	*Cnidium monnieri* (L.) Cusson.	a	Sesquiterpene	Oh et al. (2002)
Allicin	*Allium sativum* L.	Cloves	Allyl thiosulfinates	Vimal and Devaki (2004)
Kaempferol	*Rhodiola sachalinensis* A.Bor.	Roots	Phenolic compound	Song et al. (2003)
Salidroside	*Rhodiola sachalinensis* A.Bor.	Roots	Phenolic compound	Song et al. (2003)
1-O-galloyl-6-O-(4-hydroxy-3,5-dimethoxy)benzoyl-β-d-glucose	*Combretum quadrangulare* Kurz	Seeds	Gallic acid	Adnyana et al. (2001)
Picroliv	*Picrorhiza kurroa* Royle ex Benth.	a	Iridoid glycoside	Visen et al. (1991)
Indigtone	*Indigofera tinctoria* L.	Aerial parts	Aliphatic nitro-compound	Singh et al. (2001)
Acanthoic acid	*Acanthopanax koreanum* Nakai	Root bark	Diterpene	Park et al. (2004)
Myristin	*Myristica fragrans* Houtt.	a	Cetyl ester	Morita et al. (2003)
Rutin	*Artemisia scoparia* Waldst. and Kit.	a	Flavonoid	Janbaz et al. (2002)
Troxerutin	*Artemisia scoparia* Waldst. and Kit.	a	Flavonoid	Zhang et al. (2009)
Neoandrographolide	*Andrographis paniculata* (Burm.f.) Wall. Ex Nees	a	Diterpene	Chander et al. (1995)
5-0-methyl-(E)-resveratrol.3-0-β-D-glucopyranoside	*Acer mono* Maxim.	Leaves	Stilbene glycoside	Yang et al. (2005)
5-0-methyl-(E)-resveratrol.3-0-β-D-apiofuranosyl-1->6)-β-D-glucopyranoside	*Acer mono* Maxim.	Leaves	Stilbene glycoside	Yang et al. (2005)
Corilagin	*Terminalia catappa* L.	Leaves	Tannin	Kinoshita et al. (2007)
γ-Amyrone	*Sedum sarmentosum* Bunge	a	Triterpene	Amin et al. (1998)

Table 2. Cont'd.

3-epi-γ-amyrin	*Sedum sarmentosum* Bunge	a	Triterpene	Amin et al. (1998)
γ-Amyrin	*Sedum sarmentosum* Bunge	a	Triterpene	Amin et al. (1998)
18β-hydroperoxy-olean.12-en-3-one	*Sedum sarmentosum* Bunge	a	Triterpene	Amin et al. (1998)
Rubiadin	*Rubia cordifolia* L.	Roots	Anthraquinone	Rao et al. (2006)
3,4,5-trihydroxybenzoic acid	*Terminalia belerica* Roxb.	Fruit	Gallic acid	Jadon et al. (2007)
Kolaviron	*Garcinia kola* Heckel	Seeds	Biflavonoid	Biflavonoid
Kinsenoside	*Anoectochilus formosanus* Hay.	Whole plant	Furanone	Wu et al. (2007)

a, Data incomplete (derived from an abstract).

quadrangulare. Planta Med., 67(4): 370-371.
Agarwal M, Srivastava VK, Saxena KK, Kumar A (2006). Hepatoprotective activity of *Beta vulgaris* against CCl_4-induced hepatic injury in rats. Fitoterapia. 77(2): 91-93.
Ahmed B, Alam T, Khan SA (2002). Hepatoprotective activity of *Luffa echinata* fruits. J. Ethnopharmacol., 76(2): 187-189.
Ahmed B, Alam T, Varshney M, Khan SA (2002). Hepatoprotective activity of two plants belonging to the Apiaceae and the Euphorbiaceae family. J. Ethnopharmacol. 79(3): 313-316.
Ahmed B, Al-Howiriny TA, Siddiqui AB (2003). Antihepatotoxic activity of seeds of *Cichorium intybus*. J. Ethnopharmacol. 87: 237-240.
Ahmed BM, Khater RM (2001). Evaluation of the protective potential of *Ambrosia maritima* extract on acetaminophen-induced liver damage. J. Ethnopharmacol. 75: 169-171.
Ahsan MR, Islam KM, Bulbul IJ (2009). Hepatoprotective activity of Methanol Extract of some medicinal plants against carbon tetrachloride-induced hepatotoxicity in rats. Eur. J. Sci. Res. 37(2): 302-310.
Al-Howiriny TA, Al-Sohaibani MO, Al-Said MS, Al-Yahya MA, El-Tahir KH, Rafatullah S (2004). Hepatoprotective properties of *Commiphora opobalsamum* (Balessan), a traditional medicinal plant of Saudi Arabia. Drugs Exp. Clin. Res. 30: 213-220.
Ali S, Ansari KA, Jafry MA, Kabeer H, Diwakar G (2000). *Nardostachys jatamansi* protects against liver damage induced by thioacetamide in rats. J. Ethnopharmacol. 71(3): 359-363(5).
Al-Qarawi AA, Al-Damegh MA, El-Mougy SA (2003). Hepatoprotective Influence of *Adansonia digitata* Pulp. J. Herbs Spices Med. Plants 10: 3.
Amin H, Mingshi W, Hong YH, Decheng Z, Lee KH (1998). Hepatoprotective triterpenes from *Sedum sarmentosum*. Phytochem., 49(8): 2607-2610.
Anand KK, Gupta VN, Rangari V, Singh B, Chandan BK (1992). Structure and hepatoprotective activity of a biflavonoid from *Canarium manii*. Planta Med. 58(6): 493-495.
Anandan R, Devaki T (1999). Hepatoprotective effect of *Picrorrhiza kurroa* on tissue defence system in d-galactosamine-induced hepatitis in rats. Fitoterapia., 70(1): 54-57.
Aniya Y, Koyama T, Miyagi C, Miyahira M, Inomata C, Kinoshita S, Ichiba T (2005). Free radical scavenging and hepatoprotective actions of the medicinal herb, *Crassocephalum crepidioides* from the Okinawa Islands. Biol. Pharm. Bull., 28(1): 19-23.
Asha VV, Pushpangadan P (1998). Preliminary evaluation of the anti-hepatotoxic activity of *Phyllanthus kozhikodianus*, *Phyllanthus maderspatensis* and *Solanum indicum*, Fitoterapia 59: 255-259.
Asha VV, Sheeba MS, Suresh V, Wills PJ (2007). Hepatoprotection of *Phyllantus maderaspatensis* against experimentally induced liver injury in rats. Fitoterapia., 78(2): 134-141.
Babu BH, Shylesh BS, Padikkala J (2001). Antioxidant and hepatoprotective effect of *Acanthus ilicifolius*. Fitoterapia 72(3): 272-277(6).
Banskota AH, Tezuka Y, Adnyana IK, Xiong Q, Hase K, Tran KQ, Tanaka K, Saiki I, Kadota S (2003). Hepatoprotective effect of *Combretum quadrangulare* and its constituents. Biol. Pharm. Bull. 23(4): 456-460.
Beckier B (1983). The contribution of wild plants to human nutrition in Ferlo (Northern Senegal). Agroforest. Syst., 1(3): 257-267.
Bhakta T, Mukherjee PK, Mukherjee K, Banerjee S, Mandal SC, Maity TK, Pal M, Saha BP (1999). Evaluation of hepatoprotective activity of *Cassia fistula* leaf extract. J. Ethnopharmacol. 66(3): 277-282.
Bhandarkar MR, Khan A (2004). Antihepatotoxic effect of *Nymphaea stellata* Willd., against carbon tetrachloride-induced hepatic damage in albino rats. J. Ethnopharmacol., 91(1): 61-64.
Bhawna S, Kumar SU (2009). Hepatoprotective activity of some indigenous plants. Int. J. Pharm. Tech. Res. 4: 1330-1334.
Bishayee A, Sarkar A, Chatterjee M (1995). Hepatoprotective activity of carrot (*Daucus carota* L.) against carbon tetrachloride intoxication in mouse liver. J. Ethnopharmacol. 47(2): 69-74(6).

Bodakhe SH, Ram A (2007). Hepatoprotective Properties of *Bauhinia variegata* Bark Extract. Yakugaku Zasshi., 127: 1503-1507.
BR, YV, JA, NH, MG, VR (2008). Protective effect of *Phyllanthus polyphyllus* on acetaminophen induced hepatotoxicity in rats. Pak. J. Pharm. Sci., 21(1): 57-62.
Chander R, Srivastava V, Tandon JS, Kapoor NK (1995). Antihepatotoxic activity of diterpenes of *Andrographis paniculata* (Kalmegh) against Plasmodium berghei induced hepatic damage in Mastomys natalensis. Int. J. Pharmacogn., 33(2): 135-138.
Chattopadhyay RR (2003). Possible mechanism of hepatoprotective activity of *Azadirachta indica* leaf extract: part II. J. Ethnopharmacol., 89: 217–219.
Chih HW, Lin CC, Tang KS (1996). The hepatoprotective effects of Taiwan folk medicine Ham-hong-chho in rats. Am. J. Chinese Med. 24: 231-240.
Daba MH, Abdel-Rahman MS (1998). Hepatoprotective activity of thymoquinone in isolated rat hepatocytes. Toxicol. Lett., 95(1): 23-29.
Dahiru D, William ET, Nadro MS (2005). Protective effect of *Ziziphus mauritiana* leaf extract on carbon tetrachloride-induced liver injury. Afr. J. Biotechnol. 4(10): 1177-1179.
Das BK, Bepary S, Datta BK, Chowdhury AA, Ali MS, Rouf AS (2008). Hepatoprotective activity of *Phyllantus reticulate*. Pak. J. Pharm. Sci. 21(4): 333-337.
Dhanabal SP, Syamala G, Satish Kumar MN, Suresh B (2006). Hepatoprotective activity of the Indian medicinal plant *Polygala arvensis* on d-galactosamine-induced hepatic injury in rats. Fitoterapia 77(6): 472-474.
Diallo B, Vanhaelen-Fastre R, Vanhaelen M, Fiegel C, Joyeux M, Roland A, Fleurentin J (1992). Further studies on the hepatoprotective effects of *Cochlospermum tinctorium* rhizomes. J. Ethnopharmacol. 36(2): 137-142.
Dianzani MU, Muzia G, Biocca ME, Canuto RA (1991). Lipid peroxidation in fatty liver induced by caffeine in rats. Int. J. Tissue React. 13: 79-85.
Didibe M, Scheuring JF, Tembely D, Sidibe MM, Hofman P, Frigg M (1996). Baobab-homegrown vitamin C for Africa. Agrofor. Today 8: 13-15.
Du XM, Sun NY, Chen Y, Irino N, Shoyama Y (2000). Hepatoprotective aliphatic glycosides from three Goodyera species. Biol. Pharm. Bull., 23(6): 731-734.
Fakurazi S, Hairuszah I, Nanthini U (2008). *Moringa oleifera* Lam. prevents acetaminophen induced liver injury through restoration of glutathione level. Food Chem. Toxicol., 46(8): 2611-2615.
Farombi EO (2000). Mechanisms for the hepatoprotective action of kolaviron: studies on hepatic enzymes, microsomal lipids and lipid peroxidation in carbontetrachloride-treated rats. Pharmacol. Res. 42(1): 75-80.
Fleurentin J, Hoefler C, Lexa A, Mortier F, Pelt JM (1986). Hepatoprotective properties of *Crepis rueppellii* and *Anisotes trisulcus*: two traditional medicinal plants of Yemen. J. Ethnopharmacol. 16(1): 105-111.
Garg HS, Bhandari SPS, Tripathi SC, Patnaik GK, Puri A, Saxena R, Saxena RP (1994). Antihepatotoxic and immunostimulant properties of iridoid glycosides of *Scrophularia koelzii*. Phytother. Res. 8(4): 224-228.
Germano MP, Sanogo R, Costa C, Fulco R, D'angelo V, Torre EA, Viscomi MG, De Pasquale R (1999). Hepatoprotective properties in the rat of *Mitracarpus scaber*. J. Pharm. Pharmacol. 51(6): 729-734.
Gilani AH, Jabeen Q, Ghayur MN, Janbaz KH, Akhtar MS (2005a). Studies on the antihypertensive, antispasmodic, bronchodilator and hepatoprotective activities of the *Carum copticum* seed extract. J. Ethnopharmacol. 98: 127-135.
Gilani AH, Janbaz KH (1995a). Preventive and Curative Effects of *Artemisia absinthium* on acetaminophen and carbontetrachloride-induced hepatotoxicity. Gen. Pharmacol. 26(2): 309-315.
Gilani AH, Janbaz KH (1995b). Studies on protective effect of *Cyperus scariosus* extract on acetaminophen and CCl_4-Induced hepatotoxicity. Gen. Pharmacol., 26(3): 627-631.
Gilani AH, Janbaz KH, Shoaib AM (1996). Selective protective effect of an extract from *Fumaria parviflora* on paracetamol-induced hepatotoxicity. Gen. Pharmacol. 27(6): 979-983.
Gilani AH, Yaeesh S, Jamal Q, Ghayur M (2005b). Hepatoprotective activity of aqueous-methanol extract of *Artemisia vulgaris*. Phytother. Res. 19(2): 170-172.
Gupta M, Mazumder KU, Kumar ST, Gomathi P, Kumar RS (2004). Antioxidant and Hepatoprotective Effects of *Bauhinia racemosa* against Paracetamol and Carbontetrachloride induced liver damage in rats. IJPT., 3: 12-20.
Gupta NK, Dixit VK (2009). Evaluation of hepatoprotective activity of *Cleome viscosa* Linn. Extract. Indian J. Pharmacol. 41: 36-40.
Gupta SS (1994). Prospects and perspectives of natural plant products in medicine. Indian J. Pharmacol. 26: 1-12.
Gyamfi MA, Yonamine M, Aniya Y (1999). Free-radical scavenging action of medicinal herbs from Ghana: *Thonningia sanguinea* on experimentally-induced liver injuries. Gen. Pharmacol., 32(6): 661-667.
Hase K, Kasimu R, Basnet P, Kadota S, Namba T (1997a). Preventive effect of lithospermate B from *Salvia miltorhiza* on experimental hepatitis induced by carbon tetrachloride or D-galactosamine/lipopolysaccharide. Planta Med., 63(1): 22-26.
Hase K, Li J, Basnet P, Xiong Q, Takamura S, Namba T, Kadota S (1997b). Hepatoprotective principles of *Swertia japonica* on D-galactosamine/lipopolysaccharide-induced liver injury in mice. Chem. Pharm. Bull., 45(11): 1823-1827.
Hewawasam RP, Jayatilaka KAPW, Pathirana C, Mudduwa LKB (2003). Protective effect of *Asteracantha longifolia* extract in mouse liver injury induced by carbon tetrachloride and paracetamol. J. Pharm. Pharmacol., 55(10): 1413-1418(6).
Hewawasam RP, Jayatilaka KAPW, Pathirana C, Mudduwa LKB (2004). Hepatoprotective effect of *Epaltes divaricata* extract on carbon tetrachloride-induced hepatotoxicity in mice. Indian J. Med. Res., 120: 30-34.
Hinson JA (1980). Biochemical toxicology of acetaminophen. Rev. Biochem. Toxicol., 2: 103-129.
Hyun C, Jun JY, Song EK, Kang KH, Baek HY, Ko YS, Kim YC (2001). Bakuchiol: A hepatoprotective compound of *Psoralea corylifolia* on tacrine-induced cytotoxicity in Hep G2 cells. Planta Med. 67(8): 750-751.
Jadon A, Bhadauria M, Shukla S (2007). Protective effect of *Terminalia belerica* Roxb. and gallic acid against carbon tetrachloride-induced damage in albino rats. J. Ethnopharmacol., 109(2): 214-218.
Jafri MA, Jalis SM, Javed K, Singh S (1999). Hepatoprotective activity of leaves of *Cassia occidentalis* against paracetamol and ethyl alcohol intoxication in rats. J. Ethnopharmacol., 66(3): 355-361.
Jamshidzadeh A, Fereodooni F, Salehi Z, Niknahad H (2005). Hepatoprotective activity of *Gundelia tourenfortii*. J. Ethnopharmacol. 101: 233-237.
Janakat S, Al-Merie H (2002). Evaluation of hepatoprotective effect of *Pistacia lentiscus, Phillyrea latifolia and Nicotiana glauca*. J. Ethnopharmacol. 83: 135-138.
Janbaz KH, Gilani AH (1995). Evaluation of the protective potential of *Artemisia maritima* extract on acetaminophen and carbontetrachloride-induced liver damage. J. Ethnopharmacol., 47(1): 43-47.
Janbaz KH, Saeed SA, Gilani AH (2002). Protective effect of rutin on paracetamol and CCl_4-Induced hepatotoxicity in rodents. Fitoterapia., 73: 557-563.
Kadarian C, Broussalis AM, Mino J, Lopez P, Gorzalczany S, Ferraro G, Acevedo C (2002). Hepatoprotective activity of *Achyrocline satureioides*(Lam) D.C. Pharmacol. Res., 45(1): 57-61.
Kim EY, Kim EK, Lee HS, Sohn Y, Soh Y, Jung HS, Sohn NW (2007a). Protective effects of *Cuscustae semen* against Dimethylnitrosamine-Induced Acute Liver Injury in Sprague-Dawley Rats. Biol. Pharm. Bull., 30(8): 1427-1431.
Kim KH, Kim YH, Lee KR (2007b). Isolation of quinic acid derivatives and flavonoids from the aerial parts of *Lactuca indica* L. and their hepatoprotective activity *in vitro*. Bioorg. Med. Chem. Lett. 17(24): 6739-6743.
Kinoshita S, Inoue Y, Nakama S, Ichiba T, Aniya Y (2007). Antioxidant and hepatoprotective actions of medicinal herb, *Terminalia catappa* L. from Okinawa Island and its tannin corilagin. Phytomed., 14(11): 755-762.
Krishna MG, Pallavi E, Ravi KB, Ramesh M, Venkatesh S (2007). Hepatoprotective activity of *Ficus carica* Linn. leaf extract against

carbon tetrachloride-induced hepatotoxicity in rats. DARU 15(3): 162-166.
Kumar G, Sharmila BG, Vanitha PP, Sundararajan M, Rajasekara PM (2004). Hepatoprotective activity of *Trianthema portulacastrum* L. against paracetamol and thioacetamide intoxication in albino rats. J. Ethnopharmacol., 92(1): 37-40.
Kundu R, Dasgupta S, Biswas A, Bhattacharya A, Pal BC, Bandyopadhyay D, Bhattacharya S, Bhattacharya S (2008). *Cajanus cajan* Lin. (Leguminosae) prevents alcohol-induced rat liver damage and auguments cytoprotective function. J. Ethnopharmacol. 118: 440-447.
Lin CC, Huang PC (2002). Antioxidant and hepatoprotective effects of *Acathopanax senticosus.* Phytother. Res. 14(7): 489-494.
Lin CC, Lee HY, Chang CH, Namba T, Hattori, M. (1996). Evaluation of the liver protective principles from the root of *Cudrania cochinchinensis* var. gerontogea. Phytother. Res., 10(1): 13-17.
Lin CC, Lin WC, Chang CH, Namba T (1995a). Antiinflammatory and hepatoprotective effects of *Ventilago leiocarpa*. Phytother. Res., 9(1): 11-15.
Lin CC, Tsai CC, Yen MH (1995b). The evaluation of hepatoprotective effects of Taiwan folk medicine "Teng – Khia – U". J. Ethnopharmacol. 45: 113-123.
Lin SC, Lin CC, Lin YH, Shyuu SJ (1994). Hepatoprotective effects of Taiwan folk medicine: *Wedelia chinensis* on three hepatotoxin-induced hepatotoxicity. Am. J. Chin. Med. 22(2): 155-168.
Liu CT, Chuang PT, Wu CY, Weng YM, Wenlung C, Tseng CY (2006). Antioxidative and in vitro hepatoprotective activity of *Bupleurum kaoi* leaf infusion. Phytother. Res., 20 (11): 1003-1008.
Mandal SC, Saraswathi B, Ashok Kumar CK, Mohana Lakshmi S, Maiti BC (2000). Protective effect of leaf extract of *Ficus hispida* Linn. against paracetamol-induced hepatotoxicity in rats. Phytother. Res., 14(6): 457-459.
Mandayam S, Jamal MM, Morgan TR (2004). Epidemiology of alcoholic liver disease. Semin. Liver Dis., 24: 217-232.
Mankani KL, Krishna V, Manjunatha BK, Vidya SM, Jagadeesh Singh SD, Manohara YN, Raheman AU, Avinash KR (2005). Evaluation of hepatoprotective activity of stem bark of *Pterocarpus marsupium* roxb. Indian J. Pharmacol., 37(3): 165-168.
Manna P, Sinha M, Sil P (2006). Aqueous extract of *Terminalia arjuna* prevents carbontetrachloride-induced hepatic and renal disorders. BMC Complement. Altern. Med., 6: 33.
Mantena SK, Mutalik S, Srinivasa H, Subramanian GS, Prabhakar RKR, Srinivasan KK, Unnikrishnan MK (2005). Antiallergic, Antipyretic, Hypoglycemic and Hepatoprotective Effects of Aqueous Extract of *Coronopus didymus* Linn. Biol. Pharm. Bull., 28(3): 468.
Matsuda H, Morikawa T, Fengming X, Ninomiya K, Yoshikawa M (2004). New isoflavones and pterocarpane with hepatoprotective activity from the stems of *Erycibe expansa*. Planta Med., 70(12): 1201-1209.
Meera R, Devi P, Kameswari B, Madhumitha B, Merlin NJ (2009). Indian J. Exp. Biol., 47(7): 584-590.
Mitchell JR (1988). Acetaminophen toxicity. N. Engl. J. Med., 319: 1601 – 1602.
Mitchell LD, Jollow DJ, Potter WZ, Davis DC, Gillette JR, Brodie BB (1973). Acetaminophen–induced hepatic necrosis. I. Role of drugs metabolism. J. Pharmacol. Exp. Ther., 187: 185-194.
Mohammed MA, Marzouk SA, Moharram FA, El-Sayed MM, Baiuomy AR (2005). Phytochemical constituents and hepatoprotective activity of *Viburnum tinus*. Phytochem., 66(23): 2780-2786.
Mondal SK, Chakraborty G, Gupta M, Mazumder UK (2005). Hepatoprotective activity of *Diospyros malabarica* bark in carbontetrachloride intoxicated rats. Eur. Bull. Drug Res., 13: 25-30.
Morita T, Jinno K, Kawagishi H, Arimoto Y, Suganuma H, Inakuma T, Sugiyama K (2003). Hepatoprotective effect of myristin from nutmeg (*Myristica fragrans*) on lipopolysaccharide/d-galactosamine-induced liver injury. J. Agric. Food Chem., 51: 1560-1565.
Murugaian P, Ramamurthy V, Karmegam N (2008). Hepatoprotective activity of *Wedelia calendulacea* L. against acute hepatotoxicity in rats. Res. J. Agr. Biol. Sci., 4(6): 685-687.
Nguyen NT, Banskota A, Tezuka Y, Quan LT, Nobukawa T, Kurashige Y, Sasahara M, Kadota S (2004). Hepatoprotective effect of taxiresinol and (7'R)-7'-hydroxylariciresinol on d-galactosamine and lipopolysaccharide-induced liver injury in mice. Planta Med., 70(1): 29-33.
Oh H, Kim DH, Cho JH, Kim YC (2004). Hepatoprotective and free radical scavenging activities of phenolic petrosins and flavonoids isolated from *Equisetum arvense*. J. Ethnopharmacol. 95: 421-424.
Oh H, Kim JS, Song EK, Cho H, Kim DH, Park SE, Lee HS, Kim YC (2002). Sesquiterpenes with hepatoprotective activity from *Cnidium monnieri* on tacrine-induced cytotoxicity in Hep G2 cells. Planta Med., 68(8): 748-749.
Olaleye MT, Adegboye OO, Akindahunsi AA (2006). *Alchornea cordifolia* extract protects wistar albino rats against acetaminophen-induced liver damage. Afr. J. Biotechnol., 5(24): 2439-2445.
Oliveira FA, Chaves MH, Almeida FRC, Lima RCP, Silva RM, Maia JL, Brito GAC, Santos FA, Rao VS (2005). Protective effect of α- and β-amyrin, a triterpene mixture from *Protium heptaphyllum* (Aubl.) March. trunk wood resin, against acetaminophen-induced liver injury in mice. J. Ethnopharmacol., 98: 103-108.
Opoku AR, Ndlovu IM, Terblanche SE, Hutchings AH (2007). *In vivo* hepatoprotective effects of *Rhoicissus tridentata* subsp. cuneifolia, a traditional Zulu medicinal plant against carbontetrachloride-induced acute liver injury in rats. S. Afr. J. Bot., 73(3): 372-377.
Ozbek H, Ugras S, Dulger H, Bayram I, Tuncer I, Ozturk, G, Ozturk A (2003). Hepatoprotective effect of *Foeniculum vulgare* essential oil. Fitoterapia, 74(3): 317-319.
Park EJ, Zhao YZ, Young HK, Jung JL, Dong HS (2004). Acanthoic acid from *Acanthopanax koreanum* protects against liver injury induced by tert-butyl hydroperoxide or carbon tetrachloride *in vitro* and *in vivo*. Planta Med., 70(4): 321-327.
Rafatullah S, Mossa JS, Ageel AM, Al-Yahya MA, Tariq M (1991). Hepatoprotective and Safety Evaluation Studies on Sarsaparilla. Int. J. Pharmacogn. 29(4): 296-301.
Raju K, Anbuganapathi G, Gokulakrishnan V, Rajkapoor B, Jayakar B, Manian S (2003). Effects of Dried Fruits *Solanum nigrum* Linn. against carbontetrachloride-Induced Hepatic Damage in Rats. Biol. Pharm. Bull., 26(11): 1618.
Rana AC, Avadhoot Y (1991). Hepatoprotective effects of *Andrographis paniculata* against carbontetrachloride-induced liver damage. Arch. Pharm. Res., 14: 93-95.
Rao GMM, Rao CV, Pushpangadan P, Shirwaikar A (2006). Hepatoprotective effects of rubiadin, a major constituent of *Rubia cordifolia* Linn. J. Ethnopharmacol., 103(3): 484-490.
Rao KS, Mishra SH (1997). Hepatoprotective activity of the whole plants of *Fumaria indica*. Indian J. Pharm. Sci., 59(4): 165-70.
Rao KS, Mishra SH (1998). Antihepatotoxic activity of monomethyl fumarate isolated from *Fumaria indica*. J. Ethnopharmacol., 60(3): 207-213.
Rawat AKS, Mehrotra S, Tripathi SC, Shome U (1997). Hepatoprotective activity of *Boerhaavia diffusa* L. roots - a popular Indian ethnomedicine. J. Ethnopharmacol., 56(1): 61-66.
Ray D, Sharatchandra K, Thokchom IS (2006). Antipyretic, antidiarrhoeal, hypoglycaemic and hepatoprotective activities of ethyl acetate extract of *Acacia catechu* Willd in albino rats. Indian J. Pharmacol., 38(6): 408-413.
Recknagel RO (1983). A new direction in the study of carbontetrachloride hepatotoxicity. Life Sci. 33: 401-408.
Sabir SM, Rocha JBT (2008). Water-extractable phytochemicals from *Phyllantus niruri* exhibit distinct in vitro antioxidant and *in vivo* hepatoprotective activity against paracetamol-induced liver damage in mice. Food Chem., 111(4): 845-851.
Sadasivan S, Latha PG, Sasikumar JM, Rajashekaran S, Shyamal S, Shine VJ (2006). Hepatoprotective studies on *Hedyotis corymbosa* (L) Lam. J. Ethnopharmacol., 106(2): 245-249.
Sambath KR, Sivakumar T, Sivarkumar P, Nethaji R, Vijayabasker M, Perumal P, Malaya G, Upal KM (2005). Hepatoprotective and *in vivo* antioxidant effects of *Careya arborea* against carbontetrachloride-induced liver damage in rats. Intl. J. Mol. Med. Adv. Sci., 1(4): 418-424.
Sangameswaran B, Reddy TC, Jayakar B (2008). Hepatoprotective effects of leaf extracts of *Andrographis lineata* Nees on liver damage caused by carbon tetrachloride in rats. Phytother. Res., 22(1): 124-126.
Senthilkumar KTM, Rajkapoor B, Kavimani S (2005). Protective effect of

Enicostemma littorale against carbontetrachloride-induced hepatic damage in rats. Pharm. Biol., 43(5): 485-487.
Sethuraman MG, Lalitha KG, Kapoor BR (2003). Hepatoprotective activity of *Sarcostemma brevistigma* against carbon tetrachloride-induced hepatic damage in rats. Curr. Sci., 84(9): 1186-1187.
Shahjahan M, Sabitha KE, Mallika J, and Shyamala-Devi CS (2004). Effect of *Solanum trilobatum* against carbon tetrachloride-induced hepatic damage in albino rats. Indian J. Med. Res., 120: 194-198.
Shanani S (1999). Evaluation of hepatoprotective efficacy of APCL-A polyherbal formulation *in vivo* in rats. Indian Drugs. 36: 628-631.
Shim SB, Kim NJ, Kim DH (2000). β-Glucuronidase inhibitory activity and hepatoprotective effect of 18β-glycyrrhetinic acid from the rhizomes of *Glycyrrhiza uralensis*. Planta Med., 66(1): 40-43.
Singanan V, Singanan M, Begum H (2007). The Hepatoprotective Effect of Bael Leaves (*Aegle marmalos*) in alcohol induced liver injury in albino rats. Int. J. Sci. Technol., 2(2): 83-92.
Singh A, Handa SS (1995). Hepatoprotective activity of *Apium graveolens* and *Hygrophila auriculata* against paracetamol and thioacetamide intoxication in rats. J. Ethnopharmacol., 49(3): 119-126.
Singh B, Saxena AK, Chandan BK, Agarwal SG, Bhatia MS, Anand KK (1993). Hepatoprotective effect of ethanolic extract of *Eclipta alba* on experimental liver damage in rats and mice. Phytother. Res., 7(2): 154-158.
Singh B, Saxena AK, Chandan BK, Bhardwaj V, Gupta VN, Suri OP, Handa SS (2001). Hepatoprotective activity of indigtone: A bioactive fraction from *Indigofera tinctoria* Linn. Phytother. Res., 15(4): 294-297.
Song EK, Kim JH, Kim JS, Cho H, Nan JX, Soku DH, Ko GJ , Oh H, Ki YC (2003). Hepatoprotective phenolic constituents of *Rhodiola sachalinensis* on tacrine-induced cytotoxicity in Hep G2 cells. Phytother. Res., 17(5): 563-565.
Subramoniam A, Pushpangadan P (1999). Development of phytomedicine for liver diseases. Indian J. Pharmacol., 31: 166-175.
Suja SR, Latha PG, Pushpangadan P, Rajasekharan S (2003). Evaluation of hepatoprotective effects of *Rhinacanthus nasuta* root extracts. J. Trop. Med. Plants 4(2): 151-157.
Suja SR, Latha PG, Pushpangadan P, Rajasekharan S (2004). Evaluation of hepatoprotective effects of *Helminthostachys zeylanica* (L.) Hook against carbon tetrachloride-induced liver damage in Wistar rats. J. Ethnopharmacol., 92: 61-66.
Sumathy T, Subramanian S, Govindasamy S, Balakrishna K, Veluchamy G (2001). Protective role of *Bacopa monniera* on morphine induced hepatotoxicity in rats. Phytother. Res., 15(7): 643-645.
Sung SH, Won SY, Cho NJ, Gkim CY (1997). Hepatoprotective flavonol glycosides of *Saururus chinensis* herbs. Phytother. Res., 11(7): 500-503.
Szolnoki TW (1985). Food and Fruit Trees of the Gambia. Published in conjunction with the Bundesforschungsanstalt fur Forst-und Holzwirtschaft, Stiftung Walderhaltung in Afrika, Hamburg. p. 132.
Tasduq SA, Kaisar P, Gupta DK, Kapahi BK, Jyotsna S, Maheshwari HS, Johri RK (2005). Protective effect of a 50% hydroalcoholic fruit extract of *Emblica officinalis* against anti-tuberculosis drugs induced liver toxicity. Phytother. Res., 19(3): 193-197.
Tasduq SA, Singh K, Satti NK, Gupta DK, Suri KA (2006). *Terminalia chebula* (fruit) prevents liver toxicity caused by sub-chronic administration of rifampicin, isoniazid and pyrazinamide in combination. Hum. Exp. Toxicol., 25(3): 111-118.
Tuma DJ, Sorrell M (2004). Alcohol and alcoholic liver disease. Semin. Liver Dis., 24: 215
Umadevi S, Mohanta GP, Kalaiselvan R, Manna PK, Manavalan R, Sethupathi S, Shantha K (2004). Studies on hepatoprotective effect of *Flaveria trinervia*. J. Nat. Rem., 4(2): 168-173.
Van Puyvelde L, Kayonga A, Brioen P, Costa J, Ndimubakunzi A, De Kimpe N, Schamp N (1989). The hepatoprotective principle of *Hypoestes triflora* leaves. J. Ethnopharmacol. 26(2): 121-127.
Vijayan P, Prashanth HC, Vijayaraj P, Dhanaraj SA, Badami S, Suresh B (2003). Hepatoprotective effect of the total alkaloid fraction of *Solanum pseudocapsicum* leaves. Pharm. Biol. 41(6): 443-448.
Vimal V, Devaki T (2004). Hepatoprotective effect of allicin on tissue defense system in galactosamine/endotoxin challenged rats. J. Ethnopharmacol., 90(1): 151-154.
Visen PKS, Shukla B, Patnaik GK, Kaul S, Kapoor NK, Dhawan BN (1991). Hepatoprotective activity of picroliv, the active principle of *Picrorhiza kurrooa*, on rat hepatocytes against paracetamol toxicity. Drug Dev. Res. 22(3): 209-219.
Wang MY, Anderson G, Nowicki D, Jensen J (2008). Hepatic protection by *Morinda citrifolia* (noni) fruit juice against CCl_4-induced chronic liver damage in female SD rats. Plant Foods Hum. Nutr., 63(3): 141-145.
Wendel A, Feurensteins S, Konz KH (1987). Acute paracetamol intoxication of starved mice leads to lipid peroxidation in vivo. Biochem. Pharmacol., 28: 2051-2053.
WHO (1993). Regional Office for Western Pacific, research guidelines for evaluating the safety and efficacy of herbal medicines. Manila.
Wu JB, Lin WL, Hsieh CC, Ho HY, Tsay HS, Lin WC (2007). The hepatoprotective activity of kinsenoside from *Anoectochilus formosanus*. Phytother. Res., 21(1): 58-61.
Wu SJ, Wang JS, Lin CC, Chang CH (2001). Evaluation of hepatoprotective activity of Legumes. Phytomedicine 8(3): 213-219.
Xiong Q, Fan W, Tezuka Y, Ketut AI, Stampoulis P, Hattori M, Namba T, Kadota S(2000). Hepatoprotective effect of *Apocynum venetum* and its active constituents. Planta. Med., 66(2): 127-133.
Yadav NP, Dixit VK (2003). Hepatoprotective activity of leaves of *Kalanchoe pinnata* Pers. J. Ethnopharmacol., 86: 197-202.
Yang H, Sung SH, Kim YC (2005). Two New Hepatoprotective Stilbene Glycosides from *Acer mono* leaves. J. Nat. Prod. 68(1): 101-103.
Yoshikawa M, Ninomiya K, Shimoda H, Nishida N, Matsuda H (2002). Hepatoprotective and Antioxidative Properties of *Salacia reticulata*: Preventive Effects of Phenolic Constituents on carbontetrachloride-Induced Liver Injury in Mice. Biol. Pharm. Bull., 25(1): 72.
Yoshikawa M, Xu F, Morikawa T, Ninomiya K, Matsuda H (2003). Anastatins A and B, new skeletal flavonoids with hepatoprotective activities from the desert plant *Anastatica hierochuntica*. Bioorg. Med. Chem. Lett., 13(6): 1045-1049.
Zhang ZF, Fan SH, Zheng YL, Lu J, Wu DM, Shan Q, Hu B (2009). Troxerutin protects the mouse liver against oxidative stress-mediated injury induced by D-galactose. J. Agric. Food Chem., 57(17): 7731-7736.
Zhuang H, Zhang JH (2003). Epidemiology of alcoholic liver disease. Chin. J. Gastroenterol., 8: 294-297.