REVIEW ARTICLE

Hepatotoxicity and the present herbal hepatoprotective scenario

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Most of the metabolic and physiological processes of our body as well as the detoxification of various drugs and xenobiotic chemicals occur in the liver. During this detoxification process, the reactive chemical intermediates damage the liver severely. There are several commercially available drugs, consumption of which results in idiosyncratic drug reaction mediated hepatotoxicity. Drug induced hepatotoxicity is a burning problem in this regard and several drugs are withdrawn from the market due to their hepatotoxic nature. Today, worldwide search of non-hepatotoxic drugs, especially potent hepatoprotective drugs have led towards the screening of numerous herbal products. Pharmaceutical companies and scientific communities have started to consider the therapeutic efficiency of the plant-based hepatoprotective remedies. Different herbs are mentioned in various ethnopharmacological practices possessing hepatoprotective capacities and around the globe, such herbs are still used by people to cure certain liver diseases. Therefore, we have documented the various aspects of hepatotoxicity and an overview on the current scenario of the hepatoprotective herbal remedies.

Key words: Ayurveda, drug induced hepatotoxicity, ethnopharmacology, hepatoprotective, hepatotoxicity, herbal, idiosyncratic drug reactions, liver

INTRODUCTION

Liver is the largest organ of the body, contributing about 2% of the total body weight in the average adult human. Liver is associated with most of the physiological processes, which include growth, immunity, nutrition, energy metabolism and reproduction. Synthesis and excretion of bile, albumin, prothrombin and production of the compliments, which is the major effector of the humoral branch of the immune system, occurs mainly in the liver. The detoxification of the harmful chemicals occurs in the liver, which in turn, results in various hepatic diseases. Other factors causing liver damage include chronic alcoholism, viral infections, hepatocarcinoma, etc., Drug induced hepatotoxicity (DIHT) resulting in liver damage has turned into a major medical concern in recent years. During DIHT, formation of pro-inflammatory cytokines and reactive free radicals from the hepatic neutrophils and Kupffer cells cause severe oxidative stress.[1]

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Use of herbal remedies as hepatoprotective therapy has been practised in various traditional medicinal systems. A wide variety of ethnomedicinal plants, which have been claimed to be hepatoprotective in the Ayurveda, Siddha, Unani and Amchi medicinal systems as well as in other traditional medicinal practices around the globe, are successfully tested *in vivo* for their therapeutic potential. Therefore, in this review work an effort has been made to highlight the phenomenon of DIHT and the present scenario of herbal drugs and supplements, which have shown promising signs in the amelioration of the hepatic system.

THE HEPATIC SYSTEM

The hepatic system performs hundreds of metabolic and physiological process either individually or in combination with other organs of the body. Lion's share of the protein, carbohydrate and lipid metabolism is performed by the liver. It synthesises various coagulation factors, insulin-like growth factor 1, anti-thrombin, thrombopoietin, angiotensinogen and albumin. Liver is also responsible for the catabolism of bilirubin and various hormones. One of the most important functions of liver is the detoxification of toxic substances. The detoxification process itself very often damages the hepatic system. Though liver possess tremendous regenerative capacity but toxic chemicals and their metabolic intermediates often cause subclinical liver injury.

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HEPATOTOXICITY

Liver being closely associated with the gastrointestinal system receives much of the blood from the portal veins, which drains the xenobiotic compounds to the liver. In the liver, the xenobiotic compounds get activated and forms reactive metabolic species (RMS). The RMS through the oxidative stress pathway damage cellular biomolecules, cause protein dysfunctions and damage to the nucleic acids.[2] Mitochondrial dysfunction results due to RMS mediated disruption of ionic gradients and intracellular Ca^{2+} storage, causing tissue injury. Hepatocellular inflammation is another outcome of DIHT. Activated natural killer T (NKT) cells and Kupffer cells secret inflammatory mediators such as tumour necrosis factor (TNF)-α, interferon (IFN)-γ and interleukin (IL)-1β also promotes tissue damage.[3]

HEPATOTOXICITY CLASSIFICATION

Hepatotoxicity in general can be coined in the following three cases[4]: (i) the level alanine amino transferase (ALT), that is glutamyl oxalacetic acid transaminase level in the serum increases three-fold, (ii) serum alkaline phosphatase (ALP) level increases two-fold and (iii) serum bilirubin (SBLN) level is also elevated two-fold (when serum ALT and ALP levels also increases).

Hepatotoxicity is of three major classes: (a) Hepatocellular injury: When serum ALT or ALP levels are elevated; (b) Cholestatic injury: When ALP and bilirubin levels in the serum increases; (c) Mixed injury: When both the ALT and ALP levels in the serum increases.[4]

ROLE OF AYURVEDA IN HEPATOPROTECTION

The Indian Ayurvedic medicinal system dates back to the mid-second millennium BCE describing the usage of various plants based products for the ailment of numerous diseases. About 77 herbal formulations are found in Ayurveda having hepatoprotective properties,[5] among which many of them have been tested for their hepatoprotective capacity [Table 1]. Many Indian ancient medicinal texts emphasise on the hepatoprotective capacity of certain plants such as Kalmegh, (*Andrographis paniculata*), Bhuia Amla (*Phyllanthus niruri*), Indian bearberry (*Berberis aristata*), Turmeric (*Curcuma longa*), Kutki (*Picrorhiza kurroa*), Mulethi (*Glycyrrhiza glabra*), Punarnava (*Boerhavia diffusa*), Tulsi (*Ocimum sanctum*), Chicory (*Cichorium intybus*), Bhringa Raja (*Eclipta alba*), Kanak champa (*Pterospermum acerifolium*), Guduchi (*Tinispora cordifolia*), Chirayata (*Swertia chirata*), etc.

Table 1: List of some important hepatoprotective medicinal plants mentioned in Ayurveda

Family	Name of plant	Parts used in Ayurveda
Acanthaceae	*Andrographic paniculata* (Burm.f.) Wall. ex Nees	Whole plant
	Asteracantha longifolia Nees.	Leaf, root and seed
	Hygrophila spinosa T. Ander.	Leaf, root, stem and seed
Asclepiadaceae	*Hemidesmus indicus* R.Br.	Root
	Gymnema sylvestre (Retz.) R.Br.ex Schult	Leaf
	Cosmpstigma racemosa Roxb.	Root and bark
Asteracceae	*Taraxacum officinale* F.H. Wigg	Root
	Pyrenthrum indicum DC.	Flower
	Cichorium intybus L.	Whole plant
	Achille millefolium L.	Whole plant
Berberidaceae	*Berberis lycium* Royle	Leaf
Cucurbitaceae	*Bryonia alba* Wild Hops	Root
	Luffa echinata Roxb.	Fruit and seed
Euphorbiaceae	*Euphorbia neriifolia* L.	Fruit
	Phyllanthus niruri L.	Whole plant
Fumariaceae	*Fumaria officinalis* L.	Whole plant
	Fumaria parviflora Lamarck.	Whole plant
Guttiferae	*Garcinia indica* (Linn.) Robs.	Fruit
Gentianaceae	*Swertia chirata* (Wall.) C. B. Clarke	Whole plant
	Gentiana kurroo Royle	Root
Labiatae	*Mentha longifolia* (L.) Huds.	Leaf
	Hyssopus officinalis L.	Whole plant
Leguminosae	*Trigonella foenumgraececum* Linn.	Seed
	Canavalia ensiformis (L.) DC.	Root
Moraceae	*Ficus carica* L.	Fruit
	Ficus heterophylla L. f.	Root
Meliaceae	*Aphanamixis polystachya* (Wall.) R.N. Parker	Bark
Myristicaeae	*Myristica fragrans* Houtt.	Seed
Menispermaceae	*Tinospora cordifolia* (Willd.) Hook. f.	Stem
Nymphaceae	*Nelumbo nucifera* Gaertn.	Flower
Pinaceae	*Pinus roxburghii* Sarg.	Oil
Polygonaceae	*Rumex crispus* L.	Root
Rosaceae	*Prunus armeniaca* L.	Fruit
Ranunculaceae	*Paeonia emodi* Wall. ex Royle	Tuber
	Delphinium zalil L.	Whole plant
Rubiaceae	*Hedyotis corymbosa* (L.) Lam.	Leaf
Solanceae	*Lycopersicon esculentum* L.	Fruit
Umbelliferae	*Apium graveolens* L.	Seed
Verbenaceae	*Vitex negundo* L.	Whole plant
Zingiberaceae	*Zingiber officinale* Roxb.	Rhizome

At the Rajiv Gandhi Post Graduate Government Ayurvedic Hospital, Paprola, India, a clinical trial was performed, with success, to evaluate the acclaimed hepatoprotective activity of Daruharidra (*Berberis aristata*), Kamachi

(*Solanum nigrum*), Ghrita kumara (*Aloe vera*) and Bhumyamalaki (*Phyllanthus fraternus*).[6] Presently there are around 89 Ayurvedic formulations used by 37 Indian pharmaceutical companies to prepare hepatoprotective medicines.[5] The Indian Medicinal Practitioner's Co-operative Pharmacy and Stores have approved some of the drug formulations form the Ayurvedic, Siddha and Unani medicinal system[7] and they have been listed in Table 2.

PLANTS AS HEPATOPROTECTIVE RESOURCE AND THEIR RECENT PERSPECTIVES

Use of herbal medicine for the treatment of various ailments dated back to thousands of years. Out of the 250,000 higher plant species, about 70,000 species have been used in different traditional medicinal formulations.[8] Plants have emerged as a great source of pharmaceutical products. In China, the plant-based pharmaceutical industry accounts for one-third of the entire pharmaceutical business and in Malaysia, the annual market of herbal medicine is around 1 billion Malaysian ringgit. In United States alone, the estimated plant-derived pharmaceutical market is of US$9 billion per year.[9] There has been increasing scientific and industrial interest in ethnobotanical medicine during the past few decades and thus, the global market of herbal medicine is expected to increase from $19.5 billion in 2008 to $32.9 billion in 2013 with an annual growth rate of 11%.[10] Very often the synthetic drugs and antibiotics are associated with adverse effects, which include hypersensitivity, immunosuppression and allergic reactions. With the emerging cases of hepatotoxicity, antibiotic resistance in bacteria and various side effects, there is a constant need for new and effective therapeutic agents. Thus, the plant-derived bioactive chemicals have drawn the main attention as a source of complementary and alternative medicine. The use of alternative medicines for the treatment of liver diseases has a long history and medicinal plants and their derivatives are extensively used around the globe for this purpose. Huge interest of the scientific and pharmaceutical community over the therapeutic use of plant-based materials used in various ethnobotanical practices have led to purification and characterisation of various bioactive compounds, which have proven to be hepatoprotective.

Table 2: A few herbal formulations approved by indian medicinal practitioner's co-operative pharmacy and stores

Ayurvedic	Siddha	Unani
Bhringarajasava	Arumuga chendooram	Jawarish-e-Amilasada
Chandraprabhavati	Annabedhi chendooram 1 and 2	Jawarish-e-Amila luluvi
Drakahadi rasayam	Ayakantha chendooram	Jawarish-e-Tabashir
Guduchi satwam	Mandooradi kudineer	Kurs-e-gul
Jambeeradi panakam	Ayabringaraja karpam	Rue-e-amila
Panchatiktakwatha churnam	Karisalai lehyam	Sherbeth-e-anarshreen
Dhathri loham	Kantha chendooram	Sherbeth-e-deenar
Tapyadi loham	Loha mandooram	Muffarah-e-Ahmedi
Pipilyadi loham	-	Gul-e-Nilofer
Saptamiruda loham	-	Bhoi-Amla

Herbal formulations have often been found to work better in a synergistic manner than working alone. One of such formulations is LIV 52, which is a mixture of extracts from *Capparis spinosa, Cichorium intybus, Solanum nigrum, Cassia occidentalis, Terminalia arjuna, Achillea millefolium, Tamarix gallica, Eclipta alba, Phyllanthus niruri, Berberis aristata, Taphanus sativus, Phyllanthus emblica, Plumbaga zeylanica, Boerhavia diffusa, Tinospora cordifolia, Embelia ribes, Terminalia chebula* and *Fumaria officianlis*.[11] One of the earliest mentions of the much acclaimed hepatoprotective plant Milk Thistle (*Silybum marianum*) is found in the Bible (Genesis 3:18) when God tells Adam and Eve, 'thorns also and thistles shall it bring forth to thee'. Later on, silymarin, a mixture of isomeric flavolignans-silybin, silydianin and silychristen was isolated from the plant, which has proven to be beneficial in liver related disorders. Similar plants [Table 3] acclaimed in various traditional medicinal practices are now being screened for their hepatoprotective efficiencies.

HEPATOPROTECTIVE PURE ISOLATED COMPOUNDS FROM PLANT SOURCE

Recent trends in the study of hepatoprotective herbal source have turned towards isolation and purification of pure compounds from plants and assessment of their hepatoprotective activity [Table 4]:

Silymarin from *Silybum marianum,* has been a standard hepatoprotective agent for numerous studies and accounts for 180 million US dollars business in Germany alone.[86] Various bioactive compounds from plant sources possessing antioxidant, anti-cancer, immunostimulatory effect are also being tested for their possible hepatoprotective potential. A wide variety of flavonoids such as quercetin (*Helichrysum arenarium*), myricitoside C (*Cercis siliquastrum*), stachyrin (*Stachys recta*), eupatolin (*Artemisia capillaris*); alkaloids such as atropine (*Datura metel*), pilocarpine (*Aristoclochia clementis*), berberine (*Beriberis vulgaris*); organic acids and lipids such as glycolic acid (*Cynara scolymus*), dihydrocholic acid (*Curcuma longa*) have shown potent anti-hepatotoxic activity.[87]

HERBAL HEPATOTOXICITY

Not all herbs are harmless. Many cases of herbal hepatotoxicity have been reported in recent years, which include confirmations of direct hepatic fibrosis, portal

Table 3: A concise list of hepatoprotective plants

Family	Name of plant	Part	Solvent	Important parameters studied	Reference
Acanthaceae	*Thunbergia laurifolia* Linn.	Leaf	Ethanol	*In vitro, in vivo* studies; ALT, AST, TGLY, ALP, SBLN, HS, MTT	12
	Hygrophila auriculata Schumach.	Seed	Petroleum ether and methanol	*In vivo* studies; SGOT, SGPT, ALP, SD, GD, SBLN, HS	13
Asclepiadaceae	*Decalepis hamiltonii* wight. and Arn.	Root	Water	LP, PC, SOD, CAT, GPX, GR, LG, HS	14
	Tylophora indica (Burm.f.) Merr.	Leaf	Water	*in vivo* studies; AST, ALT, ALP, TB, LDH, GR, SOD, CAT, GPX, GST, LP, HS	15
Asteraceae	*Chamomile capitula*	Capitula	Hydro-ethanolic	*In vivo* studies; LG, NKA, LG, TBARS, ALP, AST, ALT, TP, SBLN, GL	16
	Artemisia absinthium Linn.	Aerial part	Aqueous	*In vivo* studies; AST, ALT, TNF-α, IL-1, SOD, GPX, MDA, HS	17
	Epaltes divaricata (L.) Cass.	Whole plant	Aqueous	*In vivo* studies; ALT, AST, ALP, LG, HS	18
Amaranthaceae	*Amaranthus spinosus* L.	Whole plant	Petroleum ether	*In vivo* studies; AST, ALT, ALP, SBLN, MDA, GSH, SOD, CAT, HS	19
	Aerva lanata Juss. Ex Schult.	Whole plant	Hydroalcoholic	*in vivo* studies; AST, ALT, ALP, SBLN	20
Apiaceae	*Apium graveolens* L.	Seed	Petroleum ether, acetone and methanol	*in vivo* studies; SGOT, SGPT, ALP, TP, TA	21
Apocynaceae	*Nerium indicum* Mill.	Flower	Methanolic extract	*in vivo* studies; AST, ALT, ALP, SBLN, SOD, MDA, HS	22
Asparagaceae	*Asparagus racemosus* Willd.	Root	Ethanol	*in vivo* studies; AST, ALT, ALP, SBLN, SOD, CAT, HS	23
	Asparagus racemosus Willd.	Whole plant	Crude extract and aqueous fraction	*in vivo*; LP, PO, TBARS	24
Bignoniaceae	*Kigelia africana* (Lam.) Benth.	Leaves	Aqueous	*in vivo* studies; ALT, AST, TBARS, SOD, CAT, GPX, DAD	25
Bixaceae	*Bixa orellana* L.	Whole plant	Methanolic extract	*in vivo* studies; SGPT, SGOT, CLT, TG, HS	26
Coclospermaceae	*Cochlospermum planchoni* Hook.f.	Rhizomes	Aqueous	*in vivo* studies; SBLN, ALP, ALP	27
Cucurbitaceae	*Momordica dioica* Roxb. ex Willd.	Leaves	Ethanolic and aqueous	*in vivo* studies; AST, ALT, ALP, SBLN, HS	28
	Trichosanthes cucumerina L.	Whole plant	Methanol	*in vivo* studies; ALT, AST, ALP, SBLN, TP, TA, LG, MDA, HS	29
Capparidaceae	*Capparis spinosa* Linn.	Root	Ethanolic	*in vivo* studies; ALT, AST, HS	30
Casuarinaceae	*Casuarina equisetifolia* L.	Whole plant	Methanolic extract	*in vivo* studies; SGPT, SGOT, CLT, TG, HS	25
Dryopteridaceae	*Arachniodes exilis* (Hance) Ching	Rhizomes	Ethanol	*in vivo* studies; SGOT, SGPT, MDA, SOD, LP	31
Euphorbiaceae	*Baliospermum montanum* Blume	Root	Alcohol and chloroform extract	*in vivo* studies; SGPT, SGOT, ALP, HS	32
	Croton oblongifolius Roxb.	Aerial part	Petroleum ether, acetone and methanol	*in vivo* studies; SGOT, SGPT, ALP, TP, TA	33
	Mallotus japonicas (L.f.) Müll. Arg.	Cortex	Aqueous	*in vivo*; AST, ALT, SD, GST, GR, GGT, MDA	34
	Phyllanthus niruri L.	Leaves and fruits	Methanol and Aqueous	*in vivo*; LP, SGOT, SGPT	35
Fabaceae	*Cajanus cajan* (L.) Millsp.	Whole plant	Methanolic	*in vivo* studies; SGPT, SGOT, AST, ALT, CLT, TG, HS	25
	Tephrosia purpurea (Linn.) Pers.	Aerial part	Aqueous-ethanolic extract	*in vivo*; AST, ALT, SBLN, ALP, LG, GGT, MDA, HS	36
	Cassia fistula L.	Leaf	N-heptane	*in vivo*; SGOT, SGPT, SBLN, ALP	37
	Cassia fistula L.	Seeds	Methanol	*in vivo*; SGOT, SGPT, ALP, SBLN	38
	Acacia confusa Merr.	Bark	Hydroalcoholic	*in vivo*; AST, ALT, MDA, CP450, SOD, GPX, HS	39
Gentianaceae	*Gentiana olivieri* Griseb.	Ariel part	Ethanol	*in vivo*; MDA, LG, AST, ALT	40
	Halenia elliptica D. Don	Whole plant	Methanol	*in vivo*; ALT, AST, ALP, SBLN, HS	41
Juncaceae	*Juncus subulatus* Forssk.	Tuber	Hydromethanolic	*in vivo*; AST, ALT, ALP, TP, TA, TGLY, MDA	42

Contd...

Table 3: Contd...

Family	Name of plant	Part	Solvent	Important parameters studied	Reference
Lamiaceae	*Orthosiphon stamineus* Benth	Leaves	Methanol extract	*in vivo*; AST, ALT, ALP, GST	43
	Hoslundia opposite Vahl	Stem	Methanol and ethyl acetate	*in vivo*; AST, ALT, ALP, SBLN	44
	Ocimum sanctum Linn	Leaf	Hydroalcoholic	*in vivo*; AST, ALT, ALP, SBLN, HS	45
Liliaceae	*Aloe barbadensis* Mill.	Aerial parts	Petroleum ether, chloroform and methanol	*in vivo*; SGOT, SGPT, ALP, SBLN, TGLY, LP, LG, G6P, and MAH, AND, HS	46
Malvaceae	*Hibiscus esculentus* Linn.	Root	ethanol	*in vivo*; SGPT, SGOT, ALP, SBLN, LP	47
	Hibiscus sabdariffa Linn.	Calyx	Aqueous	*in vivo*; ALT, AST, TBARS, SOD, CAT, GPX, DAD	25
Meliaceae	*Azadirachta indica* A. Juss.	Leaf	Hydromethanolic	*in vivo*; GPX, GST, SOD, CAT	48
Myrsinaceae	*Embelia ribes* Burm.f.	Fruit	Aqueous	*in vivo*; SGPT, SGOT, ALP, SBLN, HS	49
Nyctaginaceae	*Boerhaavia diffusa* Linn.	Root	Aqueous	*in vivo*; GOT, GPT, ACP, ALP, GD, SBLN	50
Nelumbonaceae	*Nelumbo nucifera* Gaertn.	Leaf	Ethanolic	*in vivo*; ALT, AST, ALP, GGT, SBLN, SOD, CAT, TBARS, LG	51
Piperaceae	*Piper chaba* Hunter	Fruit	Hydroacetone	*in vivo*; AST, ALT, MTT, TNF-α	52
	Piper longum Linn.	Fruits and roots	Milk extract	*in vivo*; SGOT, SGPT, ALP, SBLN	53
Pittosporaceae	*Pittosporum neelgherrense* Wt. and Arn.	Stem bark	Methanolic	*in vivo*; AST, ALT, MDA, SOD, GSH, HS	54
Ranunculaceae	*Nigella sativa* Linn.	Seeds	Aqueous-ethanolic extract	*In vitro*; GSH, ALT, AST	55
Rubiaceae	*Rubia cordifolia* L.	Roots	Aqueous extract	*In vivo*; SGOT, SGPT, GGT, ALP, HS	56
Rutaceae	*Aegle marmelos* (L.) Corr.	fruit pulp/ seeds	Aqueous extract	*In vivo*; AST, ALT, ALP, SBLN, HS	57
	Glycosmis pentaphylla Retz.	Whole plant	Methanolic extract	*In vivo*; SGPT, SGOT, AST, ALT, CLT, TG, HS	24
	Zanthoxylum armatum DC.	Bark	Ethanolic	*In vivo*; SGOT, SGPT, ALP, SBLN, TP, SOD, CAT, LG	58
Sterculiaceae	*Ptrospermum acerifolium* Linn.	Leaves	Ethanol	*In vivo*; SBLN, TP, SGOT, SGPT, ALP	59
Scrophulariaceae	*Scoparia dulcis* L.	Whole plant	Methanol, diethyl ether and petroleum ether	*In vivo*; AST, ALT, ALP, TP, GLY, LP, SOD, GR, SBLN, HS	60
	Picrorrhiza kurroa Royle ex Benth	Aqueous	Underground stem	*In vivo*; AST, ALT, LL, CLT, TGLY	61
Saururaceae	*Saururus chinensis* (Lour.) Baill.	Whole plant	Ethanol	*In vivo*; ALT, AST, MDA, SOD, TC, TGLY, CLT, TA, CE, HS	62
Salvadoracaeae	*Azima tetracantha* Lam.	Leaves	Ethanol	*In vivo*; SGOT, SGPT, SBLN, TP, ALP, TP, TA, CLT, HS	63
Umbelliferae	*Bupleurum kaoi* Liu	Roots	Ethanol	*In vivo* and *in vitro*; AST, ALT, MDA, SOD, GPX	64
Verbenaceae	*Clerodendrum inerme* (L.) Gaertn.	Leaves	Ethanol	*In vivo*; ALT, AST, ALP, TGLY, CLT	65
	Vitex trifolia L.	Leaves	Ethanolic and aqueous	*In vivo*; SBLN, TP, ALT, AST, ALP, HS	66
Vitaceae	*Vitis vinifera* Linn.	Leaves	Ethanolic, chloroform, n-butanol, water	*In vivo*; MDA, AST LT, GSH, HS	67

SGOT – Serum glutamyl oxalacetic acid transaminase; SGPT – Serum glutamyl pyruvate transaminase; SBLN – Serum bilirubin; GST – Glutathione-S-transferase; HS – Histopathological studies; GPX – Glutathione peroxidase; ALP – Alkaline phosphatase; PC – Protein carbonylation; SD – Sorbitol dehydrogenase; LP – Lipid peroxidation; GD – Glutamate dehydrogenase; SOD – Superoxide Dismutase; CAT – Catalase; AST – Aspartate amino transferase; ALT – Alanine amino transferase; LG – Liver Glutathione; TP – Total Protein; TA – Total albumin; MDA – Malondialdehyde; DAD – d-aminolevulinate dehydratase; CLT – Cholesterol; TGLY – Triglycerides; GGT – γ-glutamyl transferase; TBARS – Thiobarbaturic reacting substrate; MTT assay – MTT; GR – Glutathione reductase; NKA – Na+ K+- ATPase activity; GL – Glycogen level; TG – Total glucose; PO – Protein oxidation; MAH – microsomal aniline hydroxylase; G6P – Glucose-6-phosphatase; AND – Amidopyrine N-demethylase; CP450 – Cytochrome P450; TNF -α – Tumor Necrosis factor alpha; LL – Lipoprotein level; CE – Collagen estimation

inflammation, cholestasis, chronic hepatitis, hepatic veno-occlusive and focal hepatic necrosis. Around 60 herbal formulations have been identified as hepatotoxic in 185 recent publications[88] and the United States Drug-Induced Liver Injury Network have recognised 10% of all DIHT to be associated with intake of herbal supplements. In countries like India and China, the main problem with herbal hepatotoxicity is that the vast traditional knowledge of both the countries leads people to use herbal supplements without any prior clinical trials, which sometime turns to

Table 4: A concise list of hepatoprotective active compounds

Name of compound	Source	Family	Chemical class	Reference
α-Amyrin and β-Amyrin	*Protium heptaphyllum*	Burseraceae	Triterpene	68
Anastatin A and Anastatin B	*Anastatica hierochuntica*	Brassicaceae	Flavonoid	69
Genistein, Orobol and 5,7,4'-trihydroxy-3'-methoxyisoflavone	*Erycibe expansa*	Leguminosae	Isoflavone	70
γ-Amyrone, γ-Amyrin, 18β-hydroperoxy-olean. 12-en-3-one and 3-epi-γ-amyrin	*Sedum sarmentosum*	Crassulaceae	Triterpene	71
Rutin	*Artemisia scoparia*	Asteraceae	Flavonoid	72
Rubiadin	*Rubia cordifolia*	Rubiaceae	Anthraquinone	56
Myristin	*Myristica fragrans*	Myristicaceae	Cetyl ester	73
Naringenin and wighteone	*Cudrania cochinchinensis*	Moraceae	Flavonoid	74
Kaempferol and salidroside	*Rhodiola sachalinensis*	Crassulaceae	Phenolic compound	75
Picroliv	*Picrorhiza kurroa*	Scrophulariaceae	Iridoid glycoside	76
Gentiopicroside and Sweroside	*Swertia japonica*	Gentianaceae	Iridoid	77
Tetrahydroswertianolin	*Swertia japonica*	Gentianaceae	Xanthione	77
Mangiferin	*Salacia reticulata*	Hippocrateacaea	Phenolic compound	78
Torilin and Torilolone	*Cnidium monnieri*	Apiaceae	Sesquiterpene	79
Acanthoic acid	*Acanthopanax koreanum*	Araliaceae	Diterpene	80
18β-glycyrrhetinic acid	*Glycyrrhiza uralensis*	Fabaceae	Glycyrrhetinic acid	81
Lithospermate B	*Salvia miltorhiza*	Lamiaceae	Caffeic acid	82
Corilagin	*Terminalia catappa*	Combretaceae	Tannin	83
Neoandrographolide	*Andrographis paniculata*	Acanthaceae	Diterpene	84
Scropolioside-A	*Scrophularia koelzii*	Scrophulariaceae	Iridoid glycoside	85

be deleterious for the liver. For instance, with an estimated $400 billion market of 7000 species of Chinese herbs, at least 10 species of them have been reported to be hepatotoxic. A case of severe hepatotoxicity was reported in a 64-year-old female caused by Indian ayurvedic herbal products, Bakuchi (*Psoralea corylifolia*), Khadin (*Acacia catechu*), Bramhi (*Eclipta alba*) and Usheer (*Vetiveria zizaniodis*).[88] A detail searchable database of numerous hepatotoxic herbal supplements is given by the National Institute of Health NIH[89] Some frequently reported herbs having hepatotoxic effects are germander (*Teucrium chamaedrys*), valerian (*Valeriana officinalis*), skullcap (*Scutellaria* sp.), comfrey (*Symphytum* sp.), chaparral (*Larrea tridentata*), mistletoe (*Viscum album*), kava kava (*Pipermet hysticum*), Chinese green tea (*Camellia sinensis*), greater celandine (*Chelidonium majus*), pennyroyal (*Menthapulegium*), margosa oil (*Azadirachza indica*), borage (*Borago officinalis*), gotu kola (*Centella asiatica*), broom corn (*Sorghum vulgare*), etc.[90] Toxic alkaloids from ackee fruit (*Blighia sapida*), *Callilepsis laureola*, *Erythroxylon coca*, *Cassia angustifolia*, *Borago officinalis* and *Sassafras albidum* also have been implicated in various hepatotoxic cases. Perhaps, the most inglorious of them all is Kava Kava, which is utilised as sedative throughout the south Pacific Polynesian cultures. A toxic alkaloid pipermethystine found in the stem and the leaves of Kava demonstrated positive signs of hepatotoxicity. Many commercial herbal products such Herbalife®, Enzyte® and Hydroxy cut® have also been reported to render toxic effects on the liver and therefore, the herbal formulations too must undergo proper clinical trials before commercialising.

CONCLUSION

Maintenance of a healthy liver is essential for the overall wellbeing of an individual. Detail clinical diagnostic criteria for assessment of hepatotoxicity has already been published.[88] The clinical research has confirmed hepatoprotective efficiency of plant-based traditional and alternative medicines and guided the pharmaceutical companies to formulate numerous hepatoprotective drugs. Today, the main problem with the herbal medicines is that many herbs are consumed as polyherbal formulations where multiple herbs work synergistically. The active component responsible for the disease treatment in most cases remains unknown. Therefore, very often some other components of the polyherbal formulations adversely affect the liver. The National Poison Information Service reports that, among 785 cases of adverse reactions by herbal drugs, hepatotoxicity was the most frequent phenomenon.[91] There are proper guidelines from World Health Organisation (WHO) for the assessment of hepatiotoxicity due to herbal products.[92] A regulated research policy to highlight the advantages of hepatoprotective herbal medicine with respect to their safety and efficacy could result in a better utilisation of these complementary systems of medicine. Thus, we may conclude with the words of Dr S.T. Han,[93] 'Herbal medicine holds great but still largely unexplored potential for the development of new drugs to combat major health problems' and thus, 'mechanisms for ensuring the safety and control of herbal medicine need to be introduced as part of its formal incorporation into the health service system'.[8]

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