

Hepatotoxicity: a major complication with critical treatment

Abstract

Hepatotoxicity in one of the major parameters need to be consider in drug therapy, behind the reason that drugs given either in single or in combination for a prolonged period causes liver damage. Most of drug withdraw from the market or pending for approval due to causing hepatotoxicity (Leflunomide, Flutamide, Disulphiram, and Triglitzone) and may be chance to criticize the use based on this toxicity. Hepatoprotective agent opposes this effect while the agent who generates called hepatotoxins. There is no plant in this Universe which is non-medicinal and which cannot be made of use for many purposes and by many modes. This definition rightly suggests that in principle all plants have a potential medicinal value. Medicinal plants have been considered as important therapeutic aid for alleviating ailment of humankind. The present review is aimed at compiling data on promising Phytochemical from medicinal plants that have been tested in hepatotoxicity models using modern scientific system and mechanisms of free radicals toxicity with scavenger which revealed their toxicity belongs to synthetic or herbal product.

Keywords: liver diseases, herbal treatment, free radicals, cyp450

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Abbreviations: SGOT/AST, serum glutamate oxaloacetate transaminase; SGPT/ALT, serum glutamate pyruvate transaminase; MDA, malondialdehyde; NP-SH, non-protein sulfhydryls; ROS, reactive oxygen species; H₂O₂, hydrogen peroxide; HO[•], hydroxyl radical; RNS, reactive nitrogen species; NO, nitric oxide; PBN, alpha phenyl t-butyl nitron; CAR, constitutive androstane receptor; RXR, retinoid-x-receptor; rGSTA1/A2, glutathione s-transferase a1/a2; PPAR, peroxisome proliferator-activated receptors; CPT 1, carnitine palmitoyl transferase-1; FAO, fatty acid oxidation

Introduction

The liver is most sensitive target of xenobiotic due to its working processes such as metabolism and detoxification. Liver toxicity is a leading cause of morbidity and mortality throughout the world and increases day by day. Nearly 20,000 deaths and 2,50,000 new cases observed each year.^{1,2} Liver damage or failure is always associated with hepatocytes necrosis and elevated levels of biochemical parameters like serum glutamate oxaloacetate transaminase(SGOT/AST) and serum glutamate pyruvate transaminase (SGPT/ALT), triglycerides and malondialdehyde (MDA), non-protein Sulfhydryls (NP-SH), bilirubin and alkaline phosphatase.^{3,4} The agents responsible for hepatic trouble may be parasitic and viral infections, autoimmune diseases, genetic predisposition and intoxication with various xenobiotics such as chlorinated solvents, alcohol, alphatoxin, drugs, herbal medicines, food toxins, peroxidized oils, fungal toxins, industrial pollutants and radioactive isotopes.⁵ Most of the hepato toxic chemicals damage liver cell mainly by including lipid peroxidation, DNA damage, depletion of Sulfhydryls, altered calcium homeostasis or mitochondrial permeability transition (MPT)^{6,7} and other oxidative damages in liver. Most of drug withdraw from the market due to drug-induced liver injury (DILI)⁸ or criticize the use of many drugs, including Isoniazid, Labetalol, Trovafloxacin, Tolcapone, and Felbamate.⁹

Although tremendous scientific advancement in modern medicines, hepatic disease remains a global health problem, thus the search for new drugs is still ongoing. Hepato protectives are a class

of therapeutic agents that includes synthetic as well as natural product which offer protection to liver from damage or help in regeneration of hepatic cells. Plants are significant source of hepatoprotective drugs. It has been claimed that about 170 phyto constituents isolated from 110 plants belonging to 55 families with different genera do possess hepatoprotective activity which contain a variety of chemical constituents like phenols, coumarins, curcuminoids, lignans, essential oils and terpenoids. Clinical research has also shown that herbals have genuine utility in the treatment of liver diseases. Only a few hepato protectives are evaluated and documented used in local health traditions and pharmacological importance of these plants and their taxonomical relatives can lead to the development of invaluable plant drugs for many dreaded diseases.¹⁰ The classical systems of medicine such as Ayurveda, Siddha, Unani and Tibetan use about 1,200 plants. Random screening of plants has not proved economically effective. The present review study give evidential explore mechanism of action of medicinal plants against experimentally animal models induced hepatotoxicity and give many links to develop the future trials.

Hepatoprotective

Hepatoprotective drugs are defined as the drugs which prevent liver diseases. The literature review reveals that a large number of drugs obtained from plant are endowed with hepatoprotective claims either directly or indirectly. Hepatoprotective effects of herbal formulations as well as allopathic are studied against various toxic chemicals like alcohol CCl₄, β-Galactosamine, Thioacetamide, Paracetamol, Nimusalide, Isoniazid, Rifampicin at different dose with variant time duration which may be *in-vitro* or *in-vivo*. Most of toxicity case included oxidative stress (ROS), hydrogen peroxide (H₂O₂), hydroxyl radical (HO[•]) and peroxy radicals of biomolecules, depletion of glutathione, low production of ATP and increases permeability of cell membrane. So detoxify of ROS required antioxidant, restoring cofactors and repairing altered biomolecules therapy.¹¹⁻¹³ In the absence of reliable liver protective drugs in allopathic medical practices, herbs play important role in the management of various liver diseases. These are divided in two categories.

Synthetic hepatoprotective

There are no specific allopathic medicines used as hepatoprotective, although different research works are going on some drug like, Ursodeoxycholic acid, *S*-Adenosyl-L-methionine. Ursodeoxycholic cause decreasing immunoglobulin production by B lymphocytes as well as interleukin-1 and interleukin-2 from T lymphocytes that produced beneficial effect on plasma membrane¹⁴ and on mitochondrial oxidation,¹⁵ and recovery of liver prostaglandin level.¹⁶ It also upward regulation of glucocorticoid receptor in hepatocytes.¹⁷ Some authors believe that Penicillamine and polyphenol derivative act as metal chelator, neutralizing the pro-oxidant effect of iron, copper, lead and mercury while amphiregulin serving as anti-apoptotic action by activation of transcription-3 survival pathways, and by up-regulated Bcl-xL expression. Silymarin, *S*-adenosyl-L-methione, prostaglandin E₂ and polyunsaturated phosphatidyl choline are used as hepatoprotective due to their anti oxidant properties.^{18,19}

Herbal hepatoprotective

The medicinal plants and their derivatives with or without combination have been used as hepatoprotective from several decades, starting with the Ayurvedic treatment, and extending to the

Chinese, European and other systems of traditional medicines. Herbal drugs are recently more popular because of them are in expensive, better cultural acceptability, better compatibility, with the human body and minimal side effects.²⁰ The 21st century has shifted towards therapeutic evaluation of herbal products in the trend of the modern concept of evidence based medicinal evaluation, standardization and randomized placebo controlled clinical trials to support clinical efficacy and revealed strengths of the traditional medicinal systems. It is interesting that India is known as “Botanical Garden of the world” due to larger production of medicinal plants, more than 93 plants are used in 40 patented and proprietary multi ingredient plant formulations²¹ which include variety of chemical constituents like polyphenols (ellagic acid, gallic acid, tannins), coumarins, lignans, essential oil, monoterpenes, carotenoids, minerals (zinc, chromium, copper, manganese, iodine, selenium), saponins, glycosides, flavonoids (isoflavones, quercetin, isocatechin), organic acids, enzymes (catalase, glutathione peroxidase), vitamins (A, C, E, K), lipids, alkaloids, xanthenes, curcuminoids, and terpenoids^{5,22-25} that showing antioxidant activities (Table 1). The antioxidants may cure different diseases by protecting the cells from damage caused by free radicals having highly reactive oxygen and nitrogen containing molecules.²⁶⁻²⁹

Table 1 Plants with Phyto constituents and their screening methods

Chemical classification	Botanical name	Part used	Screening method	Phytoconstituent
Phenols	Salacia reticulata	Plant	CCl ₄	Mangiferin ³⁰
	Rhodiola sachalinensis	Root	Paracetamol	Salidroside ³¹
	Picrorrhiza kurroa	Root	CCl ₄	Picroside-I ³²
Flavonoids	Tecomella undulata	Leaves	CCl ₄	betulinic acid ³³
	Uncaria gambir	Heart-wood	CCl ₄	Catchin
	Berberis vulgaris	leaves	CCl ₄	Berberine ³⁴
Alkaloids	Fumaria indica	Plant	CCl ₄	Protopine ³⁵
	Peumus boldus	Plant	C ₄ H ₁₀ O ₄	Boldine ³⁶
	Boerhavia diffusa	Plant	Ibuprofen	Punarnavine ³⁷
Xanthines	Coffea Arabica	Seed	CCl ₄	Caffeine
Monoterpenes	Swertia japonica	Root	D-galactosamine	Tetrahydroswertia-nolin ³⁸
	Psoralea corylifolia	Plant	Tacrine	(S)-bakuchio ³⁹
Diterpens	Andrographis paniculata	Whole-plant	Ethanol	Andrographolide ⁴⁰
	Acanthopanax koreanum	Root bark	D-galactosamine	Acanthoic acid ⁴¹
Triterpens	Glycyrrhiza glabra	Roots	CCl ₄	Glycyrrhizin ⁴²
	Protium heptaphyllum	Trunk	Acetaminophen	β-Amyrin ⁴³
	Tetrapanax papyriferum	Leaves	CCl ₄	Papyriogenin A ⁴⁴
Coumarins	Solanum lyratum	Plant	CCl ₄	Scopoletin ⁴⁵
	Artemisia capillaris	Plant	D-galactosamine	Esculetin ⁴⁶
	Smilax officinalis	Roots	CCl ₄	Hesmidismine ⁴⁷
Essential oil	Anethum graveolens	Fruits	Paracetamol	α-phellandrene ⁴⁸
	Azadirachta indica	Leaves	Paracetamol	azadirachtin-A ⁴⁹
	Cynara scolymus	Plant	CCl ₄	Cynarin ⁵⁰

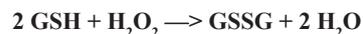
Table continued...

Chemical classification	Botanical name	Part used	Screening method	Phytoconstituent
	<i>Silybum marianum</i>	seed	Thio acetamide	Silybin ⁵¹
Lignans	<i>Thujopsis dolabrata</i>	Leaves	CCl ₄	Desoxypodophyll-otoxin ⁵²
	<i>Phyllanthus amarus</i>	Leaves	CCl ₄	Phyllanthin ⁵³
	<i>Aloe barbadensis</i>	Leaves	CCl ₄	Piceid ²¹
Glycosides	<i>Panax ginseng</i>	Rhizome	CCl ₄	Panaxoside A
	<i>Polygonum cuspidatum</i>	Roots	CCl ₄	Polydatin ⁵⁴
	<i>Mallotus japonicus</i>	cortex	CCl ₄	Bergenin ⁵⁵
Carotenoids	<i>Gardenia florida</i>	Fruits	CCl ₄	Crocin ⁵⁶
Gallic acid	<i>Terminalia bellerica</i>	Fruits	Paracetamol	Trihydroxybenzoic acid ⁵⁷
Fumaric acid	<i>Fumaria indica</i>	Whole plant	Paracetamol	Monomethyl fumarate ⁵⁸
Aliphatic nitrocompound	<i>Indigofera tinctoria</i>	Aerial parts	CCl ₄	Indigtone ⁵⁹
Tannin	<i>Terminalia catappa</i>	Leaves	CCl ₄	Corilagin ⁶⁰
Sesquiterpene	<i>Lindera strychnifolia</i>	Roots	CCl ₄	Lindstrem ⁶¹
Caffeic acid	<i>Salvia miltorhiza</i>	Roots	D-galactosamine	Lithospermate B
Furanone	<i>Anoectochilus</i>	Whole plant	CCl ₄	Kinsenoside ⁶²
Pterocarpane	<i>Erycibe expansa</i>	Stems	D-galactosamine	Erycibenin A
Allyl thiosulfates	<i>Allium sativum</i>	Bulbs	Isoniazid	Allicin ⁶³
Biflavonoid	<i>Garcinia kola</i>	Seeds	Paracetamol	Kolaviron ⁶⁴
Anthraquinone	<i>Rubia cordifolia</i>	Roots	CCl ₄	Rubiadin

Mechanism of hepatoprotective

The hepatoprotective herbal drugs act through various mechanisms to protect against various deleterious effects. By involving through one or more mechanisms, they act on the hepatocyte liver directly or indirectly and help in proper functioning the mechanism involved elevated antioxidant level/minimise generation of free radicals by Reactive Oxygen Species (ROS) as well as reactive nitrogen species (RNS), downward regulation of cytochrome 450, immuno modulative and phagocytic, preventing lipid peroxidation and enhance the level of natural antioxidant endowed body.

Source and control of ROS and RNS level: The production of oxygen based radicals is the Bane to all aerobic species. ROS and RNS generated during cellular redox process by endogenous or exogenous sources. Endogenous system included mitochondrial electron transport of aerobic respiration or by oxido reductase enzymes and metal catalyzed oxidation immune cell activation, inflammation, energy production, mental stress, excessive exercise, ischemia, infection, by vascular endothelium to neutralise nitric oxide,^{65,66} regulate cell growth and differentiation, the respiratory burst, cancer, aging while exogenous result from air and water pollution, cigarette smoke, alcohol, heavy or transition metals (Cd, Hg, Pb, Fe, As), certain drugs (cyclosporine, tacrolimus, gentamycin, bleomycin), industrial solvents. Both system works as a second messenger. Nitric oxide (NO) has been shown to serve as decreasing blood pressure⁶⁷ by vasodilation and neurotransmission through activation of soluble guanylated cyclase while Hydrogen peroxide is normally unreactive with thiols in the absence of catalyzing agents (e.g. enzymes, multivalent metals etc.), it does react with thiolate anion (S⁻), to form sulfenic acid, which in turn ionizes to form sulfenate (SO⁻). This intermediate can be reversed by the action of glutathione.⁶⁸



Cellular membranes (because of their high lipid contents) are a common target for free radicals where a free radical will capture a hydrogen moiety from an unsaturated carbon to form water. This leaves an unpaired electron on the fatty acid that is then capable of capturing oxygen, forming a peroxy radical. Lipid peroxides are unstable and decompose to form a complex series of compounds, which include reactive carbonyl compounds, such as malondialdehyde (MDA) which can react with deoxy adenosine and deoxy guanosine in DNA to form DNA adducts, primarily pyrimidol.^{69,70}

All free radical have very short half-life so evaluation of such thing is difficult therefore “trap” them by spin traps like alpha phenyl t-butyl nitron (PBN) and cyclic nitron spin traps. The molecules which antagonise the effect of free radicals called antioxidant, act by accepting or donating an electron to eliminate the unpaired condition at very low dose and final product may be water and oxygen (Figure 1). Nature has endowed us with protective antioxidant mechanisms which divided on their work like the primary defence system includes superoxide dismutase (SOD), glutathione peroxidase, catalase and thioredoxin reductase. Secondary defence’s combat processes elicited by free-radicals. Main compounds belonging to the secondary defence system are ascorbic acid (vitamin C), vitamin E (tocopherol and tocotrienols), glutathione (GSH), beta-carotene, lectoferrin or other metal containing proteins, vitamin A, NADPH and urate⁷¹⁻⁷⁵ which came from diet or not.

Melatonin (N-acetyl-5-metyoxytryptamine) is also a powerful endogenous antioxidant, have significance roles in regulation of circadian rhythms, sleep, immune system activity and elimination of oxygen free radicals^{76,77} and worked through G protein dependent

receptors which lead to the induction of anti oxidant enzyme synthesis.⁷⁸ In this way, melatonin neutralizes the effects of both oxygen and nitrogen-based reactive molecules.⁷⁹ Melatonin induces the activity of glutamyl cysteine synthetase, there by stimulating the production of another intracellular antioxidant, glutathione.⁸⁰

Inhibition of cytochrome P450: Cytochrome P450, a super family of heme-proteins metabolizes and activates many toxicologically important substrates, including ethanol, carbon tetrachloride, acetaminophen, and N-nitroso dimethyl amine, to more toxic products^{81–84} and metabolic clearance of numerous xenobiotics in the liver. They also play a critical role in the production of cholesterol, steroids, prostacyclins and thromboxane A₂. There are more than 50 CYP450 enzymes identified in humans, metabolize >90% of the clinically most important drugs.^{85,86} For example, the CYP3A enzymes metabolize over 40% of the drugs currently approved by the United

States Food and Drug Administration. Impairment of cytochrome P450 activity, which may be either genetic or environmental (inducer or inhibitor), may lead to toxicity caused by the parent compound itself. Various enzyme affected CYP450 family by up and down regulation such as- Barbiturates and chemicals that induce CYP2B initially interact with the constitutive androstane receptor (CAR) that translocate to the nucleus and dimerizes with the retinoid-X-receptor (RXR) and glutathione S-transferase A1/A2 (rGSTA1/A2). The dimer then binds to specific response elements, resulting in transcriptional activation of genes regulating P450 expression.⁸⁷ Other hand Peroxisome proliferator-activated receptors (PPAR) are members of the steroid hormone receptor super family⁸⁸ *anszxcv1*, and PPAR- α is associated with pleotropic responses induce PPAR activity, resulting in liver enlargement by stimulating the proliferation of hepatocyte peroxisomes and inducing the fatty acid oxidation enzyme CYP4A.⁸⁹

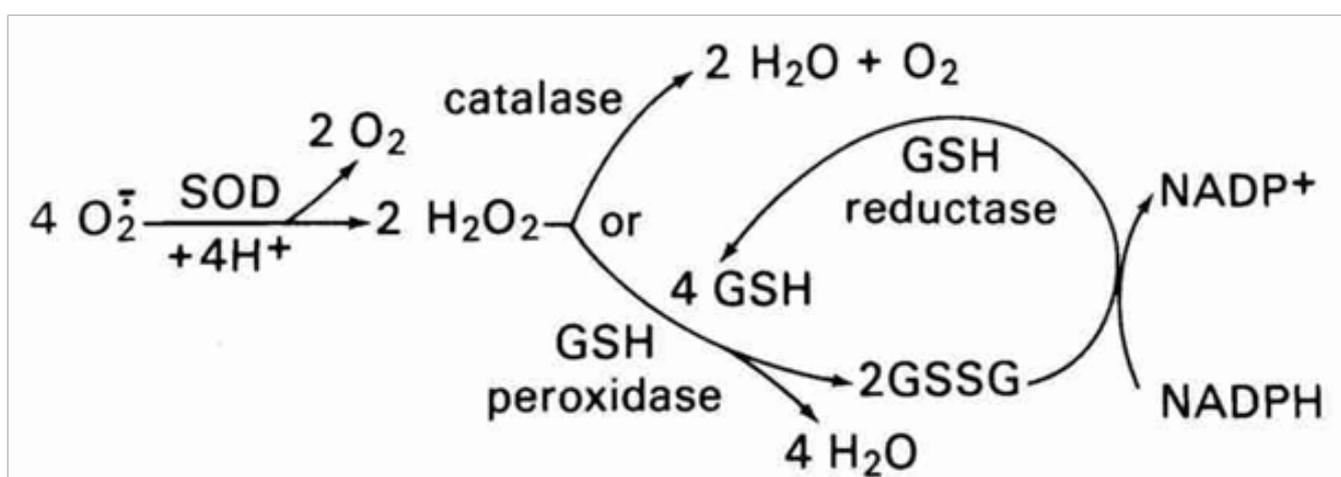


Figure 1 Scavenging activity of antioxidant molecules.

Inhibition of mitochondrial fatty acid β -oxidation: Recent studies show that tamoxifen, amlodipine and Valproic acid (VPA, or dipropylacetic acid) is an analogue of medium chain fatty acid which freely enters the mitochondrion and generates a coenzyme A ester (VPA-CoA)^{90,91} within the mitochondrial matrix. This VPA-CoA derivative can inhibit carnitine palmitoyltransferase-1 (CPT 1), an enzyme catalysing the rate limiting step of the mitochondrial entry and β -oxidation of long-chain fatty acids.⁹² Furthermore, the generation of the VPA-CoA ester reduces mitochondrial levels of CoA, which is a cofactor mandatory for fatty acid oxidation (FAO). A second mechanism which could play a major role in VPA-induced inhibition of FAO is the cytochrome P450 (CYP)-mediated generation of D4-VPA.^{93,94} Indeed this metabolite also enters the mitochondrion to generate D2, 4-VPA-CoA, a reactive metabolite able to covalently bind to (and thus inactivate) FAO enzymes but above hypotheses are controversy.

Regulation of Interleukin 6 pathway: IL-6, pro-mitogenic and anti-apoptotic in nature for hepatocytes having both to delay and accelerate liver regeneration by down regulate Jak/STAT activation, e.g., transforming growth factor, granulocyte/macrophage colony-stimulating factor (GM-CSF), and angiotensin II.^{95–97} When IL-6 binds to its soluble receptor, sIL-6r, which binds to the gp130 receptor, resulting in the activation of Janus Kinase (JAK). This leads to activation of the MAPK pathway and activation of Stat3 by tyrosine

(Y) phosphorylation. Homo dimerized Stat3⁹⁸ is able to translocate into the nucleus and activate gene transcription. In the liver, this process promotes liver regeneration,⁹⁹ the acute-phase response and hepato protection against Fas and toxic damage.^{100–102,97}

Conclusion

Several medicinal plants are now prevalent for the treatment of various liver diseases. Most of them are potential hepatogenic/hepatoprotective against hepatotoxicity. They are considering as high safety margin, efficacy and cost effectiveness. Although different herbal drugs are used from long times ago but no precise their mechanism of action. While Considering the enormous biodiversity resources of India and coordinated research involving biomedical scientists, nutritionist, scholars working the field of pharmacology, therapeutics.

Pharmacognosy and other health professionals provided a big chance to develop evidence based alternative medicine to cure different kinds of liver diseases, included various pathways and molecules with their action. Research on free radicals and antioxidants involving these is one such effort in the right direction. This may be beneficial in the era of hepatoprotective.

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Conflict of interest

The author declares no conflict of interest.

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