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Review Article

Mechanisms involved in hepatoprotection of different herbal products: A Review

Anil Kumar[1], Nishant Rai*[1], Navin Kumar[1], Pankaj Gautam[1], Kumar J.S[2]

[1]Department of Biotechnology, Graphic Era University, Dehradun, Uttarakhand, India
[2]Department of Biotechnology, SBS PG Institute of Biomedical Sciences and Research, Balawala, Dehradun, Uttarakhand, India

ABSTRACT

Since ancient time, herbal products are being used for health remedies. These plant products are in continuous demand and have an edge over other products in the area of drug discovery and therapeutics due to their high efficacy, safety and easy availability. Although herbal drugs are available for almost all ailments, hepato-protective drugs have unique importance. Since liver being one of the most vital organs responsible for nutrient metabolism, digestion, storage, excretion, drug metabolism and detoxification, its toxicity is major problem and caused by different compounds like carbon tetrachloride, thioacetamide which damage the hepatocytes and affect liver functioning by acting through generation of oxidants, ROS or inhibition of Cytochrome p450 activity, etc. Different herbal products representing different plant parts are able to act as hepatoprotective drugs by minimizing or preventing the hepatotoxicity through many mechanisms. The primary induction of hepatotoxicity is inducing level of liver enzymes as serum glutamate pyruvate transaminase (SGPT), Serum glutamate oxalo transaminase (SGOT), alkaline phosphatase (ALT), total Bilirubin, MDA, total protein, SOD, and CATS. Most of the mechanism of antioxidants is to decrease the elevated level of liver enzymes in serum via different mechanism and in case of liver toxicity to stop the lipid peroxidation. Hepatoprotective herbal drugs thus have far reaching effects in preventing the liver damage and more such drugs are being sought and more precise mechanism of action is being investigated.

Keywords: Antioxidants; Glutathione; Hepatoprotection; Hepatotoxicity; Inhibition of Cytochrome p450; Liver enzymes; MDA.

INTRODUCTION

Liver is not only the largest organ based on size but also the body part with high rate of metabolic activity. It is one of the most vital organs that functions as a common centre of nutrient metabolism, digestion, storage and excretion of the products. Over that, liver is integral part of drug metabolism and removal of xenobiotics from the body thus protecting against foreign substances by detoxifying and eliminating them. Various chemotherapeutic agents like carbon tetrachloride, thioacetamide etc. during their metabolism inside the liver cause severe damage to hepatocytes. Since time, immemorial mankind has made the use of plants in the treatment of various ailments. The Indian traditional medicine like Ayurveda, Siddha and Unani and extending to the Chinese, European and other systems of traditional medicines are predominantly based on the use of plant materials. Herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. The association of medical plants with other plants in their habitat also influences their medicinal values in some cases. One of the important and well documented uses of herbal products is as hepatoprotective (Mohamad Saleem *et al*., 2010).

In the last decade there has seen a paradigm shift towards therapeutic evaluation of herbal products in liver disease models by carefully synergizing the strengths of the traditional systems of medicine with that of the modern concept of evidence-based medicinal evaluation and standardization to support clinical efficacy (Thyagarajan *et al.,* 2002). Medicinal Plants have a very important place as they maintain the health and proper functioning of different organs, including liver without causing any toxic side effects.

Liver diseases are among the most serious ailment. They may be classified as acute or chronic hepatitis (inflammatory liver diseases), hepatosis (non- inflammatory diseases) and cirrhosis (degenerative disorder resulting in fibrosis of the liver). Liver diseases are mainly caused by toxic chemicals (certain antibiotics, chemotherapeutics, peroxidized oil, aflatoxin, carbontetrachloride, chlorinated hydrocarbons, etc.) excess

* Corresponding Author
Email: nishantrai1@gmail.com
Contact: +91-9719020412
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Table 1: Some important herbal plants with their hepatoprotective mechanism

S.N.	Plant/parts	Toxicity	Dose	Biochemical Parameters						Proposed mechanism of hepatoprotective	References
				SGPT	SGOT	ALP	T.Bi	MDA	Misc.		
1	Ficus carica linn (Moraceae)	CCl_4	500 mg/kg	+	+	+	+	+	-	Production of antioxidant Inhibition of Cytochrome P450s Reduction of peroxidant.	Venkatesh *et al*., 2007
2	Rootsof-Hemides-mus indicus	PCM/ CCl_4	100-500 mg/kg	+	+	+	+	-	Direct Bil.	Rduction of peroxidation	Baheti *et al*., 2006
3	Aerial part of Plumbago zeylania	CCl_4	100 mg/kg	+	+	+	+	-	-	Inhibition of Cytochrome P450s.	Kumar *et al.,* 2009
4	Seed of Bixa orellana, etc.	CCl_4	500mg /kg	+	+	-	+	-	Choles-terol& Glucose	Glutathione mediated detoxification Radical suppressing activity.	Islam *et a*l., 2009
5	Leaves of leucas cili-ate.	CCl_4	400 mg/kg	+	+	+	+	-	-	Production of antioxidant.	Qureshi *et al.,* 2010
6	Aleovera Eclipta alba, etc	PCM	500 mg/kg	+	+	+	+	-	Albumin	Reduction of oxidation Increasing glutathione level.	Parmar *et al.,* 2010
7	Polyherbal formula-tion, liv52, etc.	PCM	500 mg/kg	+	+	+	-	-	-	Due to antioxidant	Koner *et al*., 2009
8	Prak-20	CCl_4	-	+	+	+	-	-	-	Production of antioxidant	Prakash *et al*., 2010
9	leaves of *Urtica dioica* L.	CCl_4	400 mg/kg	+	+	+	+	+	SOD	Antioxidant mechanisms	KatakiS-arma Man-jir *et al*., 2012
10	*Flaveria trinervia*	Ethanol	500 mg/kg	+	+	+	+	+	SOD/CAT	Enhancement of peroxidation	V.Krishna *et al*., 2012

+ : test performed, - : test not performed

consumption of alcohol, infections and autoimmune disorder. Most of the hepatotoxic chemicals damage liver cells mainly by inducing lipid peroxidation and other oxidative damages in liver. Enhanced lipid peroxidation produced during the liver microsomal metabolism of ethanol may result in hepatitis and cirrhosis (Kumar *et al.*, 2011).

Hepatoprotective herbs

Herbal drugs for liver disorders have been in use for several decades. Despite showing the significant efficacy and less side effects liver diseases, in particular, they are still not acceptable treatment modalities (Mohamad Saleem *et al*., 2010). Until recently, it was acceptable like a dogma that no effective treatment of liver diseases exists. However, with the discovery of a plethora of drugs of plant origin, the situation has now markedly changed and substantial volume of evidence indicates that these drugs exert a specific influence on the hepatic system. The traditional medicine refers to a broad range of ancient natural healthcare practices including practices as well as Ayurveda, Siddha, Amchi Chinese, Unani, etc. Although experimental evaluations have been done on many plants and on their formulations, only some plants have clearly shown the anti hepatotoxic activity against liver diseases (Pandey, 2011; Kashaw Varsha, *et al*., 2011) (Fig.1). Medicinal plants have a very important place as they not only maintain the health and vitality of human beings and animals but also cure several diseases, including liver disorder without causing any toxicity. India is the largest producer of medicinal plants and is rightly called the "Botanical Garden of the world" (Ward and Daly, 1999). There are numerous plants and traditional formulations available for the treatment of liver diseases. Some of the important herbal plants with their hepatoprotective mechanism are shown in table 1. About 600 commercial herbal formulations with claimed hepatoprotective activity are being sold all over the world. Around 170 phytoconstituents isolated from 110 plants belonging to 55 families have been reported to possess hepatoprotective activity. In India, more than 93 medicinal plants are used in different combina-

tions in the preparation of 40 patented herbal formulations (Koner *et al*., 2009).

Mechanism of Hepatoprotection

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 hepatocytes/liver directly or indirectly and help in proper functioning. The mechanisms include an increase in antioxidant level/decrease in oxidants (ROS formation), inhibition of cytochrome P450s, increase and decrease level of Liver enzymes, reduced peroxidation / Lipid peroxidation (MDA), and increase in level of glutathione or reducing equivalents.

Increase in antioxidant level/decrease in oxidants (ROS formation)

Antioxidants are substances that at relatively low concentrations are able to compete with other oxidizable substrates and, thus, to significantly delay or inhibit the oxidation of these substrates. Thus, these antioxidant molecules in cells can act either by free radical neutralization or by inhibiting their formation (Halliwell and Gutteridge, 1989). It is evident that several phytoconstituents have the ability to induce microsomal enzymes either by accelerating the excretion of the hepatotoxin or by inhibition of lipid peroxidation induced by it (Mehta *et al.*, 1999). Phytoconstituents like flavonoids, triterpenes, saponins and alkaloids are known to possess hepatoprotective activities (Xiong *et al.*, 2003 and Singhai *et al.*, 2011). Flavonoids, tannins and microelements have been suggested to act as antioxidants and exert their antioxidant activity by scavenging the free radicals, which cause lipid peroxidation (Muriel *et al*., 2008).

Several enzymes are present, which help in facilitating protection from oxidants by inhibiting/neutralizing the ROS formation like superoxide dismutase (SOD), Catalase, Peroxidases (Glutathione peroxidases) (Singh *et al*., 2011) (Fig.1). Antoxidant enzymes also help by detoxifying lipid peroxidation products (glutathione S-transferases, glutathione peroxidases and ascorbate peroxidase). A network of low molecular weight antioxidants (ascorbate, glutathione, etc.) along with enzymes (mono dihydro ascorbate reductase, dehydroascorbate reductase and glutathione reductase) is needed for the regeneration of the active forms of the antioxidants (Droge, 2002 and Kumar Vivek *et al.,* 2011).

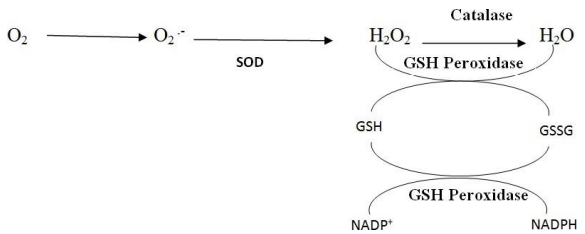

Figure 1: Mechanism of Antioxidant and oxidants (ROS formation)

Inhibition of cytochrome P450

Plant cytochromes P450 are involved in a wide range of biosynthetic reactions, leading to various fatty acids conjugates, plant hormones, defensive compounds, or medically important drugs. Terpenoids, which represent the largest class of characterized natural plant compounds, are often substrates for plant CYPs (Rittle *et al.*, 2010**)**. The remarkable reactivity and substrate promiscuity of P450s have long attracted the attention of chemists (Chefson *et al.*, 2006). Recent progress towards realizing the potential of using P450s towards difficult oxidations have included: (i) eliminating the need for natural co-factors by replacing them with inexpensive peroxide containing molecules, (ii) exploring the compatibility of p450s with organic solvents, and (iii) the use of small, non-chiral auxiliaries to predictably direct P450 oxidation (Chefson *et al.*, 2007).

The cytochrome p 450 system is actively involved in metabolism of many drugs and xenobiotics and help in their elimination from the body. This enzyme is polymorphic in nature of different forms involved in drug metabolism. Cytochrome P450s are generally located in the endoplasmic reticulum (ER) and with the help of coenzyme, NADPH reductase catalyzes the two electron reduction of molecular O_2 to H_2O. The most common reaction catalyzed by cytochromes P450 is a monooxygenase reaction, e.g., insertion of one atom of oxygen into an organic substrate (RH) while the other oxygen atom is reduced to water (Sigel *et al*., 2007).

$$RH + O_2 + NADPH + H^+ \rightarrow ROH + H_2O + NADP^+$$

Cytochrome p450 (CYP1A1) is present in the mitochondria of liver tissue. The enzyme is targeted to the mitochondria by proteolysis of cryptic MT-targeting signals, which remove a certain number of amino acids from the NH_2 terminus, thus producing two alternative truncated isoforms of mitochondrial CYP1A1 (mt1A1) (Tsatsakis *et al.,* 2009). The active site of cytochrome P450 contains a haem iron center. The iron is tethered to the P450 protein via a thiolate ligand derived from a cysteine residue. This cysteine and several flanking residues are highly conserved in known CYPs. Because of the vast variety of reactions catalyzed by CYPs, the activities and properties of the many CYPs differ in many aspects (Meunier *et al.*, 2004)**.** However, CYP450s and other enzymes can also bioactivate chemicals, converting them to reactive products that modify cellular constituents and produce damage (Guengerich *et al*., 2005 and Guengerich, 2006). In contrast to the P450s involved in sterol metabolism in normal physiological condition, the levels of the xenobiotic-metabolizing CYP450s vary widely, and individuals can be completely lacking these because of mutation. In an individual deficient of the particular CYP450 (poor metabolizer), limited metabolism of the particular drug will result in the toxic accumulation of the drug or its metabolites (Kuntze 1989; Rofiee *et al.,* 2011).

Increase and decrease level of Liver enzymes

Hepatic cells participate in metabolic activities and contain a variety of enzymes. In tissue, separate aminotransferase (AST) and alkaline aminotransferase (ALT) were found to be in higher concentrations in a cytoplasm, and AST exists in mitochondria. In liver injury, transport function of the hepatocytes gets disturbed, resulting in the leakage of plasma membrane and thereby causing an increased enzyme level in serum. The elevated activities of these enzymes are indicative of cellular leakage and the functional integrity of the cell membranes in liver. ALP is excreted by liver via bile in the liver injury due to hepatotoxins, which results in a defective excretion of bile by the liver and is reflected in their increased levels in serum (Tatiya *et al.,* 2012). Hepatotoxins produce varying degrees of damage to the liver. They may produce a variety of morphological changes, which may be typical of the various agents. Liver damage is usually associated with elevation in the serum levels of many biochemical markers such as AST, ALT, ALP, bilirubin, triglycerides and cholesterol (Peter A Akah *et al* 2010). CCl4 is commonly used to induce hepatotoxicity in animal models. Metabolic processes convert $_{CCl4}$into the trichloromethyl radical (CCl_3-) which interacts with O_2 to yield the highly reactive trichloromethylperoxy radical ($CCl_3O_2^-$). Both radicals are capable of binding to proteins and lipids or abstracting a hydrogen atom from unsaturated lipids, which induces lipid peroxidation and leads to changes in the endoplasmic reticulum, reduction in protein synthesis, and elevation of serum transaminase enzyme levels. The significant increase in the serum marker enzymes *viz*, AST, ALT and ALP and decrease in the level of albumin and total protein has been observed in $_{CCl4}$-treated rats.

Reduced peroxidation / Lipid peroxidation (MDA)

The massive production of reactive species may lead to depletion of protective physiological moieties glutathione, tocopherols, etc. The depletion of these low molecular weight antioxidants further propagate the peroxidation and alkylation causing the chain reaction to proceed and finally damage to the membrane function and structure (Baheti *et al.,* 2006**)**. One of the end products formed following membrane damage is malondialdehyde (MDA) and their increased in level suggests enhanced lipid peroxidation, which may lead to tissue damage and may be as a consequence or failure of antioxidant defense mechanisms to prevent the formation of excessive free radicals (Dash *et al.,* 2007).

Increase in level of glutathione or reducing equivalents

The glutathione protects hepatocytes by combining with the reactive metabolite of paracetamol thus preventing their covalent binding to liver proteins. The non-enzymic antioxidant, glutathione is one of the most abundant tripeptides present in the liver. Its functions are mainly concerned with the removal of free radical species such as hydrogen peroxide, superoxide radicals, alkoxy radicals, and maintenance of membrane protein thiols and as a substrate for glutathione peroxidase and GST (Dash *et al.*, 2007; Balasubramanian, 2011; Das *et al*., 2012**).**

CONCLUSION

Hepatoprotective herbal drugs have inherent property of safety, efficacy and cost effectiveness in general and preventing the damage of liver in particular. These drugs act through various mechanisms and maintain the functionality of important organ. Although different herbal drugs are available in the market, their precise mechanism of action is not well understood. More in-depth studies are required to know about various pathways and molecules involved in their action.

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