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Liver Toxicity and its Amelioration by Natural Antioxidants - A Review

Muzafar Ahmad Sheikh[1] and Manju Tembhre[2]
[1]Department of Zoology, Govt. Degree College Ganderbal, Jammu & Kashmir - 191201, India
[2]M K Ponda College, Bhopal - 462 038, India
Email: muzafar7923@gmail.com
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Abstract

Antioxidants are extensively present in natural sources from food and medicinal plants. Various natural antioxidants, especially polyphenols, flavonoids, vitamin E and carotenoids exhibit a wide range of biological effects including hepatoprotection, anti-inflammatory, anti-aging, anti-atherosclerosis and anticancer. The present paper provides information on the main resources and hepatoprotective efficacy of natural antioxidants against liver toxicity with special emphasis on liver biomarkers and antioxidant enzymes.

Keywords: ALT, AST, ALP, SOD, CAT, GST, Hepatoprotection, Antioxidants, Herbs.

Introduction

The liver is the largest and most important internal organ in the body, which plays vital roles of secretion, metabolism, storage, synthesis, excretion and detoxification of several compounds. The liver is an important site of drug metabolism and removal of xenobiotics from the body thus protects against foreign substances by detoxifying and eliminating them. Various toxic agents like carbon tetra-chloride, alcohol, some drugs etc. during their metabolism inside the liver cause severe damage to hepatocytes and develop hepatic ailments. Most of the hepatotoxic chemicals damage liver cells mainly by inducing lipid peroxidation and other oxidative damages in liver, which many a time becomes fatal. Therefore, hepatic disease and injury are still some of the major global health issues. The serum enzymes are very important adjuncts to clinical diagnosis of diseases and tissue injury. Hepatic injury by toxicants results in the leakage of cellular bio-markers into the bloodstream, resulting in increased levels of serum alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) and bilirubin (Reddy and Lokesh, 1996). These serum parameters are well established hepatotoxicity biomarkers. In addition GGT, Albumin, Ammonia, Cholesterol and Urinobilinogen are also considered as the responsive biomarkers used in the diagnosis of liver diseases. Body cells are equipped with a number of endogenous antioxidant defense machinery, which includes superoxide dismutase (SOD), catalase (CAT), glutathione (GSH) and glutathione peroxidase (GPX) (Beckman and Ames, 1998). In the excess, toxicants are major cause of oxidative stress resulting in the decline of these antioxidants involved in body's defense system. Hence the measurement of these parameters is indicative of pathological condition.

It has been demonstrated that wide range of plants contain variety of antioxidant phytochemicals or bioactive molecules which can neutralize free radicals and decrease the oxidative stress that plays a critical role in the incidence of adverse toxic effects associated with liver disease (Beydilli *et al.,* 2015). Therefore, herbal drugs have gained importance and popularity in recent years because of their safety, efficacy and cost effectiveness. There is wealthy scientific data that shows hepatic disorders can be alleviated upon dietary intake or supplementary intake of natural antioxidants (Sen *et al.*, 2007; Selvan *et al.* 2008; Hazra *et al*., 2010). Antioxidants are defined as substances that inhibit or delay the oxidation of biologically relevant molecules either by specifically quenching free radicals or by chelation of redox metals. Dietary intake contains variety of antioxidants and vitamin supplements those play a vital role in hepatoprotection in variety of liver ailments (Li *et al.*, 2015). Many naturally occurring antioxidants have ability to ruin oxidation of proteins, lipid peroxidation and prevent production of reactive oxygen species (ROS), thus act as important therapeutic agents to oxidative stress (OS), acting as free radical scavengers, quenchers of singlet oxygen and reducing agents (Baiano and Nobile, 2015). This review is aimed at summarizing the effects of various antioxidants found in medicinal plants on liver biomarkers and antioxidants that have demonstrated utility in improving liver diseases.

Antioxidants

The exogenous or natural antioxidants are chiefly derived from food and medicinal plants, such as cereals, fruits, vegetables, flowers, spices, mushrooms, beverages, traditional medicinal herbs and agricultural by-products from the industries processing (Fu *et al*., 2011; Deng *et al.,* 2012; Li *et al.,* 2014). Based on their chemical composition and mode of action these natural antioxidants from plant materials are mainly categorized as direct antioxidant, indirect antioxidant and metabolic antioxidants.

Direct antioxidant are redox active, short-lived and often interferes directly with oxidation by interacting with the

free radicals that cause it, leading to harmless metabolites. They act upon direct chemical (nonenzymatic) scavenging of ROS generated free radicals and some of them are recycled with endogenous oxidoreductases or via intracellular reducing shuttles (Dinkova-Kostova and Talalay, 2008). Direct antioxidant chemically contains aryl amines and indoles-carotene, lycopene polyenes-carotene, retinol, selenium containing compounds ebselen. polyphenols-flavonoids, stilbenes, and hydroquinone, monophenols, tocopherols (vitamin E), 17-estradiol (estrogen), 5-hydroxytryptamine (serotonin) (Li *et al.,* 2014 a & b; Zill-e-Huma *et al.,* 2009; Breithaupt, 2004).

Indirect antioxidants activate the body to produce its own antioxidants or otherwise improve the actions of direct antioxidants. Indirect antioxidants act catalytically, are not consumed, have long half-lives and are unlikely to evoke pro-oxidant effects and may or may not be redox active. Indirect antioxidants are mostly composed of amino oxidase inhibitors, calcium antagonists, dopamine receptor agonists, glutamate receptor antagonists, ion chelators, nitric oxide synthase inhibitor. They help prevent cytotoxicity, ROS and free radical generation targeting inhibitors and receptors deregulating metal homeostasis (Tumer *et al.,* 2015).

Metabolic antioxidant is chemically consisting of N-acetyl-cysteine, glutathione, 2-oxothiazolidine-4-carboxylate and other thiol delivering compounds N-butyl--phenylnitrone. Carnitine, creatine, lipoic acid (thioctic acid), ubiquinone and idebenone. These antioxidants quash cellular injury caused by free radicals by reducing secondary metabolic burden over cellular organelle viz. mitochondria (Xu *et al.,* 2017).

Hepatoprotection by natural antioxidants present in medicinal plants

Medicinal plants and their derivatives continue to play a central role in the maintenance and protection of health of large proportions of the world's population. In recent years, interest has shifted in using natural products for pharmacological purposes, as a form of complementary or replacement therapy. The role of some herbal products and phytonutrients in the hepatoprotection is summarized in table-1 and described below.

Wheat germ oil (WGO) has been reported as a natural source of antioxidants with protective role in hepatic toxicity. Administration of WGO for 6 weeks to albino rats having sodium nitrate-induced hepatotoxicity elicit significant decrease in alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP) in comparison with their increased levels in sodium nitrate treated groups of rats (Anwar and Mohamed, 2015). The presence of biologically active components (unsaturated fatty acids, unsaponifible matters and sterols matters) in WGO acts as antioxidant and cyto-protective by stimulating estrogen secretion and inhibiting oxidative damage (Vecera*, et al.,* 2003) suggests role of WGO as a natural protective antioxidant agent in hepatic tissues.

Grapeseed oil supplementation offers a great advantage for therapeutic purpose to minimize diazinon (DZN) free radical induced cell damage and may be attributed to the antioxidant role of its constituents. The levels of serum ALT (+71.2%), AST (+70.7%) and ALP (+117.8%) were statistically increased, while the level of serum total protein (-20.0%) was significantly decreased in rats exposed to DZN compared with control and other treated groups. However, combined treatment of grapeseed oil and DZN to rats produced significant decrease in the levels of ALT (+10), AST (+25.0%) and ALP (+26.5%) in comparison with DZN treated rats (Al-Attar, 2015). Damage of hepatocytes by DZN is reflected by elevated levels of hepato specific enzymes (ALT, AST and ALP), these are cytoplasmic in location and are released into circulation after cellular injury (Sallie *et al.,* 1991). The study of Al-Attar (2015) showed that grape seed oil supplementation alleviated the extensive changes in enzymatic profiles in rats exposed to DZN. Similarly, oral administration of grapeseed oil to rats with CCl_4- induced hepatotoxicity protected the liver from CCl_4 damage (Maheswari and Rao, 2005). Grape seeds are rich in flavan-3-ol, including proanthocyanidins and catechins (Rodríguez *et al*., 2006). They contain high concentration of polyphenol proanthocyanidins, which are the oligomers of flavan-3-ol units including catechin and epicatechin (Weseler and Bast, 2017).

Methanolic extract of rhizome of *Curculigo orchioides* and aqueous extract of whole plant of *Epaltes divaricata* offer protection to elevated levels of AST, ALT and ALP in CCl_4-challenged rat and mice (Venukumar and Latha, 2002; Hewawasam *et al.,* 2004). The alcoholic extract of whole plant of *Solanum trilobatum* brings significant decrease in the activities of alanine transaminase (ALT), aspartate transaminase (AST) and alkaline phosphatase (ALP) in the group of rats with CCl_4-induced hepatotoxicity. Lipid peroxidation (LPO) was augmented significantly with simultaneous decline in the activities of glutathione peroxidase (GPx), catalase (CAT) and superoxide dismutase (SOD) in liver tissue in the CCl_4 treated rats. Administering the alcoholic extract *Solanum trilobatum* in these rats rendered the levels of the above mentioned parameters to near normal levels (Shahjahan *et al.,* 2004).

Upadhyay *et al.* (2004) authenticated the antioxidant activity of aqueous leaf extract of medicinal herb *Aegle marmelos* in rats challenged with alloxan. The alloxan significantly decreased the level of GSH. But, after supplying the animals with *Aegle marmelos* leaf extract at the dose of 500 mg/kg body weight along with alloxan for duration of four weeks, the investigators observed that there was a significant increase in the GSH levels than that of only alloxan treated group of rats.

Table - 1: Hepatoprotective effects of some medicinal plants and their derivatives in Rat/mice. (Alanine aminotransferase (ALT), Aspartate transaminase (AST), alkaline phosphatase (ALP), reduced glutathione (GSH), Glutathione peroxidase GPx, Catalase (CAT), Superoxide dismutase (SOD) and Lipid peroxidation (LPO).

S. No.	Scientific name of herb/plant	Part /extract used	Toxicant	Liver Biomarkers/antioxidant enzymes studied	References
1	*Curculigo orchioides*	Methanolic extract of rhizome	CCl_4	AST, ALT and ALP	Venukumar and Latha, 2002
2	*Epaltes divaricata*	Aqueous extract of whole plant	CCl_4	AST, ALT and ALP	Hewawasam *et al.,* 2004
3	*Solanum trilobatum*	Alcoholic extract of whole plant	CCl_4	ALT, AST, ALP, GSH, SOD, CAT, GPx and LPO	Shahjahan *et al.*, 2004
4	*Aegle marmelos*	Aqueous extract of leaf	Alloxan	GSH	Upadhya *et al.,* 2004
5					
6.	*Albizzia lebbeck*	Aqueous leaf extract	Alloxan	SOD, CAT, GSH, GPx and GST.	Resmi *et al.*, 2006.
7	*Ichnocarpus frutescens*	Chloroform and methanolic extracts of whole plant	Paracetamol	ALT, AST, ALP, total protein, bilirubin, GSH, SOD and CAT.	Dash *et al.,* 2007
8	*Urtica urens*	Hexane extract of seeds	CCl_4	ALT, AST, CAT, GST and LPO	Sen *et al.*, 2007
9	*Artanena sesamoides*	Methanolic extract of aerial parts	Streptozotocin (STZ)	SGOT, SGPT, ALP & LPO	Selvan *et al.* 2008
10	*Pongamia pinnata*	Aqueous and ethanol extracts of leaves	Acetaminophen	SGOT, SGPT, ALP and total bilirubin, SOD, CAT and GPx	Rajeshkumar and Kayalvizhi , 2015
11	*Spilanthes ciliate, Rhinacanthus nasuta* and *Lxora coccinea* roots	Ethanolic extract of whole plant and roots.	Aflatoxin B1	SGOT, SGPT, ALP and reduced glutathione (GSH)	Shyamal *et al.,* 2010
12	*Melia azedarach*	Ethanolic extract of leaves	Simvastatin	SGOT, SGPT, ALP and total bilirubin and total protein.	Rao *et al.,* 2012
13	*Marsilea minuta*	Methanolic extract of whole plant	CCl_4, paracetamol and ethanol	(AST), (ALT), (ALP), total bilirubin, direct bilirubin, triglycerides, cholesterol, glucose, creatinine, albumin, and total protein.	Balne *et al.,* 2013
14	*Andrographis paniculata*	Aqueous leaf extract.	CCl_4	AST, ALT, ALP, total bilirubin and total protein	Nasir *et al.,* 2013.

S. No.	Scientific name of herb/plant	Part /extract used	Toxicant	Liver Biomarkers/antioxidant enzymes studied	References
15	*Emblica officinalis*	Methanolic fruit extract	Iron	ALT, AST, ALP, bilirubin, LPO	Sarkar *et al.*, 2013
16	*Bauhinia variegata*	Ethanolic extract of roots	CCl_4	AST, ALT, ALP and total protein.	Prabha *et al.,* 2014.
17	*Taraxacum officinale* and *Colocasia esculenta*	Ethanolic leaf extract	CCl_4	AST, ALT, ALP, total bilirubin, total protein, SOD, CAT, GSH and LPO	Sheikh, 2014.
18	*Coleus amboinicus*	Ethanolic leaf extract	….	…	Ahirwar *et al.,* 2015.
19	Grape seed oil	Seeds	Diazinon	ALT, AST, ALP, Cholestrol	Al-Attar, 2015
20	Wheat germ oil	Seeds	Sodium nitrate	ALT, AST, ALP	Anwar and Mohamed, 2015
21	*Taraxacum officinale*	Ethanolic leaf extract	….	….	Sheikh *et al.,* 2015
22	*Coleus amboinicus*	Ethanolic leaf extract	CCl_4	AST, ALT, ALP, total bilirubin and total protein	Ahirwar and Tembhre, 2016.
23	*Rosmarinus officinalis*	Ethanolic extract of upper shoot	….	…	Akram *et al.,* 2016
24	*Monodora myristica*	Aqueous extract of seeds	Cadmium	ALT, AST, ALP, GSH, CAT, SOD and cholesterol	Oyinloye *et al.,* 2016
25	*Olea europaea* L., *Nigella sativa, Sesamum indicum*	Seeds	Diazinon	ALT, AST, ALP, GSH, SOD and total bilirubin	Al-Attar *et al.,* 2017

Dash *et al.* (2007) studied the hepatoprotective and antioxidant effects of *Ichnocarpus frutescens* whole plant in wistar albino rats intoxicated with paracetamol (750 mg/kg). During the study, the authors used two solvents viz. chloroform and methanol for extraction of the plant material by soxhlation. They measured the degree of protection by using biochemical parameters like ALT, AST, ALP, serum bilirubin, total protein, lipid peroxidation (LPO), glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT). It was found that chloroform and the methanol extracts at dose levels of 250 mg/kg and 500 mg/kg produced statistically significant ($P<0.05$) liver protection by decreasing the levels of serum enzymes, bilirubin and lipid peroxidation, however, the levels of Glutathione (GSH), superoxide dismutase (SOD) and catalase (CAT) were significantly increased in a dose dependent manner. The results obtained by using extracts were comparable with the standard drug, silymarin.

Resmi *et al.* (2006) evaluated the antioxidant nature of aqueous extract of *Albizzia lebbeck* leaves in alloxan induced diabetic rats. The researchers estimated the levels of thiobarbituric acid reactive substances (TBARS) and reduced glutathione (GSH) in liver. Activities of antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione S transferase (GST) were appraised in all experimental groups of animals. They found that alloxan significantly decreased the levels of SOD, CAT, GPX and GST. However, the extract of *Albizzia lebbeck* leaves significantly restored the altered levels of these parameters to near normal levels in rats exposed to alloxan.

Rajeshkumar and Kayalvizhi (2015) evaluated the antioxidant and hepatoprotective effect of *Pongamia pinnata* leaves in rats inebriated with acetaminophen. The investigators used ethanol and water as the solvents for the extraction of the plant material. The activities were determined by comparing the biochemical parameters like SGOT, SGPT, ALP and total bilirubin, SOD, CAT and GPx of plant extract treated group with acetaminophen treated group. From their study, it was clear that the ethanolic extract (300 mg/kg b. w.) showed the most significant hepatoprotective and antioxidant activities and was

comparable with standard drug silymarin. The aqueous extract (300 mg/kg b. w.) also showed the fair amount of protection.

Jackie *et al.* (2010) evaluated the antioxidant effect of ethanolic extract of *Etlungera elatior* flower in lead exposed rats. They assessed the antioxidant potential of the extract of the flower. The extract was also tested for the presence of various phytochemical classes of compounds such as alkaloids, phenolic compounds, flavonoids, tannins and saponins using standard procedures of analysis. They further assayed lipid peroxidation, SOD, glutathione peroxidase (GPx) and glutathione-s-transferase (GST). The results lead them to formulate that the extract is having excellent antioxidative potential.

Shyamal *et al.* (2010) evaluated the antihepatotoxic effect of ethanol extract of three medicinal herbs viz. whole plant of *Spilanthes ciliate, Rhinacanthus nasuta* roots and *Lxora coccinea* roots in rats intoxicated with aflatoxin B1. They checked the antihepatotoxic properties of these plant parts by analyzing various biomarkers viz. SGOT, SGPT, ALP and reduced glutathione (GSH) in various groups of animals and compared the results thus obtained with the group treated with the standard drug silymarin for knowing the percentage of recovery with the ethanol extracts.

The exposure of rats to Simvastatin (20 mg/kg. p.o) resulted in significant changes in biochemical parameters (increases in SGOT, SGPT, ALP, serum bilirubin and decrease in total protein content). The restoration of the said parameters towards normal was seen when the rats were given the ethanolic extract of *Melia azedarach* leaves at the selected doses of 300 mg/kg and 500 mg/kg (Rao *et al.,* 2012). This could be due to presence of many important phytochemical components such as alkaloids, carbohydrates, flavanoids, glycosides, saponins in the leaves of *Melia azedarach* (Krishnaiah and Prashanth, 2014).

The hepatic damage was tempted in different sets of rats by administering 1:1 v/v CCl_4 in olive oil 1ml/kg b.w. p. o. 3g/kg.b.w.p.o paracetamol and 5g/kg b.w. p.o ethanol. The toxicity was evaluated by estimating the serum biochemical parameters viz. AST, ALT, ALP, total bilirubin, direct bilirubin, triglycerides, cholesterol, glucose, creatinine, albumin, and total protein. It was found that CCl_4, paracetamol and ethanol resulted in the clinically significant alterations in the levels of above biomarkers. However, the methanolic fraction (50 mg/kg b.w. and 100 mg/kg b.w.) toluene fraction (50 mg/kg b.w. and 100 mg/kg b.w.) n-butyl alcohol (50 mg/kg b.w. and 100 mg/kg b.w.) of *Marsilea minuta* whole plant restored significantly the altered levels of these biomarkers in a dose dependent manner (Balne *et al.,* 2013).

Nasir *et al.* (2013) substantiated the protective nature of aqueous leaf extract of *Andrographis paniculata* in CCl_4 exposed rats. Their study was based upon the estimation of various biochemicals like AST, ALT, ALP, total bilirubin and total protein in different groups of experimental rats. The free radical scavenging activity of the extract was determined by analyzing the levels of GSH and LPO in various experimental groups of rats. They found that CCl_4 exposure significantly raised the serum levels of AST, ALT, ALP, total bilirubin and LPO (in homogenate), however, the levels of total protein in serum and GSH in homogenate were decreased. The extract of *Andrographis paniculata* showed ameliorative efficacy by bringing the altered levels of these parameters towards normal.

The abnormal high levels of serum ALT (103.63%), AST (126.1%), ALP (155.66%) and bilirubin (244.05%) due to iron-overloaded hepatic damage in cells were markedly reduced by oral administration of methanolic fruit extract of *Emblica officinalis* in mice to approach the normal control values. Further the lipid peroxidation product was significantly enhanced (75%) in liver homogenates of iron-intoxicated mice compared with normal mice, which was significantly declined with *Emblica fficinalis*. These restorative alterations in these parameters prove the good antioxidant capacity of *Emblica officinalis* (Sarkar *et al.,* 2013).

In another study we evaluated the hepatoprotective and antioxidant effects of *Taraxacum officinale* and *Colocasia esculenta* in wistar albino rats intoxicated with CCl_4 (Sheikh, 2014). The hepatoprotective study revolved around the estimation of serum ALT, AST, ALP, ACP, total bilirubin and total protein. As far as the assessment of antioxidant efficacy of two herbs was concerned, it was covered by estimating the levels of SOD, CAT, GSH and LPO in liver homogenate. We found that CCl_4 elevated the levels of ALT, AST, ALP, ACP, total bilirubin and LPO but decreased that of SOD, CAT, GSH and total protein highly significantly ($p<0.001$). However, the treatment of rats with the ethanolic extracts of the above two herbs at two doses of 100 mg/kg and 200 mg/kg each for the duration of 30 days daily restored the altered levels of these biomarkers to near normal levels in a dose dependent manner. It was found that ethanolic extract of *Taraxacum officinale* offered the more protection than that of *Colocasia esculenta.* This may be due to presence of more active ingredients in *Taraxacum officinale.* The phytochemicals of in *Taraxacum officinale*, which shows antioxidant properties, are found in both the roots and leaves. The leaves contain bitter sesquiterpene lactones, such as taraxinic acid, and triterpenoids, such as cycloartenol, taraxasterol **(1)** and -taraxasterol **(2)**. The roots, in addition to these compounds, contain phenolic acids, inulin and others sesquiterpenes, including the eudesmanolides, tetrahydroridentin B **(3)** and taraxacolide-glucopyranoside **(4)**; the guaianolides,13-dihydrolactucin and ixerin D; three germacranolide esters, taraxinic acid -glucopyranoside **(5)**, its 11,13-dihydroderivative **(6)** and ainslioside **(7)** and various triterpenes, their acetates and 16-hydroxy derivatives (Kisiel and Barszcz, 2000; WHO, 2007; Gonzalez-Castejon *et al.*, 2012). However it has been reported that *Colocasia esculenta* mainly contain calcium oxalate,

fibers, minerals (calcium phosphorus, etc.), and starch, vitamin A, B, C, etc. in its leaves (Sheth, 2005) Phytochemically, these also contain flavones, apigenin, luteolin and anthocyanins (Khare *et al*., 2007).

Ahirwar *et al.* (2016) explored the *in vitro* antioxidant efficacy, total phenolic and total flavonoid contents of *Coleus amboinicus* leaves. They found that the ethanolic extract of *Coleus amboinicus* contain sufficient amount of natural antioxidants, good phenolic and flavonoid contents which the pharmaceutical companies can separate in order to make the potent drugs. Apigenin is a naturally occurring flavonoid which was reported to be present in the plant *Coleus amboinicus* (Yoganarasimhan, 1996). The essential oil *Plectranthus amboinicus* possesses a significant antioxidant property due to the presence of phytochemical compounds such as Carvocrol and Thymol. Non-enzymatic antioxidant-reduced glutathione was found to be increased in the *P. amboinicus* essential oil treated mice. The use of essential oil of *P. amboinicus* is cheaper than natural drug formulation and also without any side effects on the animal model (Manjamalai and Grace, 2012). Ahirwar and Tembhre (2016) studied the protective potential of ethanolic extract of *Coleus amboinicus* in rats intoxicated with CCl_4. Their study was purely based on the estimation of biomarkers like ALT, AST, ALP, ACP, total bilirubin and total protein. They found that CCl_4 exposure (2 ml/kg b. w., i. p. weekly) elevated the levels of serum ALT, AST, ALP, ACP and total bilirubin while as decreased that of total protein significantly. However, the levels of these parameters were retrieved significantly to near normal when rats were supplied with the ethanolic extract of *Coleus amboinicus* leaves at 200 mg/kg b. w daily for 30 days.

Aqueous seeds extract of *M. myristica* significantly protect the rat liver against toxicity exerted by cadmium. There was an elevation ($P < 0.05$) in the activities of hepato-specific enzymes; ALP, ALT and AST and reduction ($P < 0.05$) in the hepatic enzymatic and non-enzymatic antioxidants (GSH, CAT and SOD) in the cadmium treated group. Treatment with *M. myristica* seed extract at doses 200 and 400 mg/kg b.w. showed a significant reduction ($P < 0.05$) in the levels of ALP, ALT and AST and enhancement in GSH level as well as SOD and CAT activities (Oyinloye *et al.,* 2016). Cadmium being non-redox metal is capable of indirectly eliciting oxidative damage to the liver by depleting cellular antioxidant levels especially glutathione and depleting protein-bound sulfhydryl groups; which promotes the generation of reactive oxygen species (ROS) such as superoxide ion, hydroxyl radicals and hydrogen peroxide (Wang *et al.,* 2015). The presence of alkaloids, saponins, tannins, flavonoids, cardiac glycosides and phenols in varying quantity in the aqueous extract of *M. myristica* seeds shows strong antioxidant activity which can ameliorate hepatocellular damage caused by cadmium intoxication in experimental rats in a dose dependent manner by improving the antioxidant defense systems as well as mitigating lipid peroxidation associated with cadmium toxicity.

In another investigation we (Sheikh *et al.,* 2015) evaluated the *in vitro* antioxidant activity of *Taraxacum officinale* leaves using ethanol as the solvent. We found that the extract is having fair amount of phytochemicals like alkaloids, terpenoids, flavonoids, glycosides, phenolic compounds, carbohydrates, saponins and proteins. We used DPPH and reducing power assays in determining the antioxidant activity of the extract and came up with the conclusion that the same possess the significant potential in combating the rampaging free radicals. The ethanolic extract of *Rosmarinus officinalis* upper shoot part contained good amount of total phenolic and total flavonoid contents. The extract was good enough in neutralizing the free radicals as depicted by the DPPH and reducing power assays (Akram *et al.,* 2016). The main phenolic acid in *Rosmarinus officinalis* was found to be rosmarinic acid (Shan *et al.,* 2005).

Prabha *et al.* (2016) examined the liver protective effect of *Bauhinia variegate* roots in albino wistar rats exposed to CCl_4. The investigators used various parameters for assessing the protection like AST, ALT, ALP and total protein. They found that CCl_4 significantly elevated the levels of these parameters indicating the liver toxicity. The ethanolic root extract of *Bauhinia variegate* at 200 mg/kg b. w. and 400 mg/kg b. w. exhibited highly significant ($p<0.01$) reduction in the levels of these parameters signifying its protective effect.

Sheikh and Tembhre (2016) also exposed the free radical scavenging activity of *Colocasia esculenta* ethanolic leaf extract using DPPH and reducing power assays. They noticed the presence of various phytochemicals like saponins, alkaloids, terpenoids, flavonoids, carbohydrates, glycosides, amino acids, tannins and phenolic compounds in the extract. They found that the extract is good enough to quench the free radicals, which may be attributed to the phytochemicals present in it. The antioxidant activity of phenolic compounds mainly depends on their redox properties such as adsorbing and neutralizing free radicals, quenching singlet and triplet oxygen, or decomposing peroxides. In general, flavonoids have higher antioxidant activities against peroxyl radicals than do phenolic acids due to multiple hydroxyl groups.

The recent study of Al-Attar *et al.* (2017) on the effect of olive (*Olea europaea* L.), sesame (*Sesamum indicum*) and black seed oils (*Nigella sativa*) on diazinon-induced hepatotoxicity in male rats showed their hepatoprotective efficacy. DZN, treatment to rats caused a remarkable increase in the level of serum AST (+49.0%), ALP (+59.6%), GGT (+178.4%), bilirubin (+69.3%) as compared to controls. In rats subjected to combination of sesame oil plus DZN the level of serum bio-markers were statistically restored in comparison to DZN-treated rats and were AST (+19.80%), ALP (+30.9%), GGT (+35.6%), bilirubin (77.2 %). However, insignificant changes in the

level of these enzymes and total bilirubin were noticed in rats treated with olive oil plus DZN and black seed oil plus DZN. These results suggest that these oils possess preventive factors against the toxicity of DZN due to its antioxidant properties. Further the Levels of serum GSH (43.7%) and SOD (31.1%) were statistically decreased in rats treated with DZN, which were improved with application of sesame oil plus DZN viz. GSH (24.2%) and SOD (9.7%). No significant alterations in levels of serum GSH and SOD were observed in rats treated with olive oil plus DZN and black seed oil plus DZN. The results of Attia and Nasr (2009) study showed that black seed oil has ability to neutralize dimethoate-induced changes in biochemical parameters and lipid peroxidation by activation of the antioxidant defense system in rats.

The aforementioned herbal extracts exhibited strong hepatoprotective and antioxidant activities and the bioactive compounds present in these extracts have the potential to be developed into natural ameliorative and antioxidant agents that may have applications in animal and human health.

Conclusion and future study

Based on the reviewed literature, it is obvious that herbs possess potential application to protect from acute and chronic diseases, due to their high antioxidant activity. This review presents abundant data on hepatoprotective and antioxidative activities of herbs, as well as information related to their chemical contents. Hepatoprotective herbal drugs have inherent property of safety, efficacy and cost effectiveness in general and preventing the damage of liver in particular. This review also presents a strong body of evidence that different parts of medicinal herbs or plants consumption can reduce or even eliminate the harmful effects on drug induced liver toxicity or ailments.

Future study requires gene therapy to produce more antioxidants in the body, genetically engineered plant products with higher level of antioxidants, novel biomolecules, synthetic antioxidant enzymes (SOD mimics) and the use of functional foods enriched with antioxidants. Also more in-depth studies are mandatory to know about various pathways and molecules involved in their action.

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