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Screening of some Traditionally Used Plants for Their Hepatoprotective Effect

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1. Introduction

Liver is one of the largest organs in human body and the chief site for intense metabolism and excretion (Ram, 2001). It has a surprising role in the maintenance, performance and regulating homeostasis of the body. It is involved with almost all the biochemical pathways responsible for growth, fight against disease, nutrient supply, energy provision and reproduction (Ward & Daly, 1999). The major functions of the liver are carbohydrate, protein and fat metabolism, detoxification, blood coagulation, immunomodulation, secretion of bile and storage of vitamin.

Two major types of reactions occur in the liver in the presence of exogenous substances. The first involve chemical modification of function groups by oxidation, reduction, hydroxylation, sulfonation and dealkylation. Various enzymes including mixed oxidases, cytochromes P-450, and the glutathione *S*-acyltransferases are involved in such biochemical transformations that usually lead to inactivation of drugs. This step is usually followed by conversion of the resulted metabolites into more water-soluble derivatives that are excreted in the bile or urine via coupling with glucuronate, sulfate, acetate, taurine or glycine moieties (Ram, 2001).

Liver damage inflicted by hepatotoxic agents is of grave consequences (Subramoniam & Pushpangadan, 1999). Liver ailments represent a major global health problem (Baranisrinivasan et al., 2009). Liver cirrhosis is the ninth leading cause of death in the USA (Kim et al., 2002). Toxic chemicals, xenobiotics, alcohol consumption, malnutrition, anaemia, medications, autoimmune disorders (Marina, 2006), viral infections (hepatitis A, B, C, D, etc.) and microbial infections (Sharma & Ahuja, 1997) are harmful and cause damage to the hepatocytes. Hepatotoxic chemicals cause damage to the liver cells mainly by inducing lipid peroxidation and other oxidative events (Dianzani et al., 1991).

In spite of the tremendous advances in modern medicine, no effective drugs are available, which stimulate liver functions and/or offers protection to the liver from damage or help to regenerate hepatic cells (Chatterjee, 2000). In the absence of reliable liver protective drugs in modern medicine, there exists a challenge for pharmaceutical scientists to explore the potential of hepatoprotective activity of plants based on traditional use (Witte et al., 1983). A large number of medicinal preparations are recommended for the treatment of liver disorders (Chatterjee, 2000) and quite often claimed to offer significant relief. Study of many traditional plants used for liver problems led to the discovery of active compounds yet developed to successful drugs. Silymarin (Morazzoni & Bombardelli, 1995), schisandrin B (Cyong et al., 2000), phyllanthin, hypophyllanthin, picroside I and kutkoside (Ram, 2001) are examples of natural antihepatotoxic compounds derived from traditional herbs. About 600 commercial preparations with claimed liver protecting activity are available all over the world. About 100 Indian medicinal plants belonging to 40 families are components of liver herbal formulation (Handa et al., 1986). The effectiveness of most of these plant products must be scientifically verified to identify new medicaments for the management of liver disorders.

2. Silymarin, the standard antihepatotoxic drug

Silymarin, the collective name for an extract from milk thistle, *Silybum marianum* (L.) Gaertneri, is a naturally occurring flavonolignan. Silymarin is a mixture of stereoisomers mainly silybin (also called silybinin, silibin or silibinin) representing 80%, w/w of silymarin. Other minor stereoisomers include isosilybin, dihydrosilybin, silydianin and silychristin (Wagner et al., 1968). Silymarin protects experimental animals against the hepatotoxin α-amanitin (Hahn et al., 1968) and has a strong antioxidant property (Comoglio et al., 1990). Other reported biological properties of silymarin include inhibition of LOX (Fiebrich & Koch, 1979a) and PG synthetase (Fiebrich & Koch, 1979b). For decades, silymarin has been used clinically in Europe for the treatment of alcoholic liver disease and as antihepatotoxic agent (Salmi & Sarna, 1982). Silymarin is well tolerated and largely free of adverse effects (Comoglio et al., 1990). Silymarin act as an antioxidant by scavenging preoxidant free radicals and by increasing the intracellular concentration of glutathione (GSH). It also exhibits a regulatory action of cellular membrane permeability and increase its stability against xenobiotics injury, increasing the synthesis of ribosomal RNA by stimulating DNA polymerase-I, exerting a steroid like regulatory action on DNA transcription and stimulation of protein synthesis and regeneration of liver cells (Dehmlow et al., 1996; Saller et al., 2007). Silymarin efficacy is not limited to the treatment of toxic and metabolic liver damage; it is also effective in acute, chronic hepatitis and in inhibiting fibrotic activity (Saller et al., 2007). It acts as inhibitor of the transformation of stellate hepatocytes into myofibroblasts, this process is responsible for the deposition of collagen fibres leading to cirrhosis (Fraschini et al., 2002).

3. Induction of liver toxicity in experimental animals

In order to study the hepatoprotective effect of plant extracts or pure isolates it is necessary to induce liver toxicity in experimental animal models. The reported protocols for induction of liver toxicity varying greatly in terms of the used liver toxin, doses, duration and route of administration. Below is a collection of the most common experimental procedures use by different groups.

3.1 Carbon tetrachloride-induced liver toxicity

Liver damage induced by carbon tetrachloride is the most commonly used model for the screening of hepatoprotective drugs (Slater, 1965). The rise in serum levels of Glutamic

Pyruvate Transaminase (SGPT), Glutamic Oxaloacetic Transaminase (SGOT) and cholesterol following carbon tetrachloride has been attributed to the damaged structural integrity of the liver cells. These components are cytoplasmic in location and released into circulation after cellular damages (Sallie et al., 1991). Carbon tetrachloride also plays a significant role in inducing triacylglyceral accumulation, depletion of GSH, depression of protein synthesis and loss of enzymes activity (Recknagel et al., 1989). Carbon tetrachloride induces hepatotoxicity in rats following its metabolic activation in the hepatocytes. Therefore, it selectively causes toxicity in the liver cells while maintaining semi-normal metabolic function. Carbon tetrachloride is metabolically activated by the cytochrome P-450 dependent mixed oxidease in the endoplasmic reticulum to form trichloromethyl free radical ($\cdot CCl_3$) and $\cdot Cl_3COO$ which combined with critical cellular macromolecules, cellular lipids and proteins in the presence of oxygen to induce lipid peroxidation (Snyder & Andrews, 1996). Some of the lipid peroxidation products are reactive aldehydes, e.g., 4-hydroxynonenal, which can form adducts with proteins (Weber et al., 2003). These consequences lead to changes in the structures of the endoplasmic reticulum and other membranes hence to increase in plasma membrane permeability to Ca^{2+} resulting in a severe disturbances of calcium homeostasis and consequently necrotic cell death (Weber et al., 2003). The loss of metabolic enzyme activation, reduction of protein synthesis and loss of glucose-6-phosphatase activation, all lead to liver injury (Recknagel & Glende, 1973; Azri et al.,1992). In addition to the intracellular events, Kupffer cell activation can contribute to liver injury (elSisi et al., 1993). Kupffer cells are resident macrophages of the liver which constitute approximately 80% of the fixed macrophages in the body (McCuskey, 2006). They may enhance liver injury by oxidant stress (elSisi et al., 1993) or TNF-_ generation, which may lead to apoptosis (Shi et al., 1998). In more than 70% of the reviewed published data liver toxicity were experimentally induced by Carbon tetrachloride. However, the experimental procedures were considerably different.

3.1.1 Single dose carbon tetrachloride-induced liver toxicity

Acute liver toxicity can be induced by a single dose of carbon tetrachloride. However, the route of administration and dose are different from one research group to another. Intraperitoneal injection seems to be the most commonly used method for carbon tetrachloride administration due to the ease of handling and rapid onset of action. Rats are usually a popular experimental animal model and the reported doses were 3 ml/kg (Jamshidzadeh et al., 2005), 2.5 ml/kg (Sen et al., 1993; Nishigaki et al., 1992), 2 ml/kg (Channabasavaraj et al., 2008), 1.5 ml/kg (Bhadauria et al., 2009), 1.25 ml/kg (Rafatullah et al., 2008) or 0.5 ml/kg (Rao et al., 1993). In most cases, carbon tetrachloride is diluted with oils (1:1). The large variation in doses may arise from weather the stated volumes represented the volume of pure carbon tetrachloride or the total volume of the mixture. If this is the case, the wide range of doses from 3- 0.5 ml will shrink to 1 ml (1.5- 0.5 ml). In case of using mice as the experimental animal model the reported carbon tetrachloride doses were much less (0.01, 0.016. 0.02 and 0.03 ml/kg) (Amat et al., 2010; Suzuki et al., 1990; Zhou et al., 2010; Wang et al., 2008).

Induction of liver toxicity via oral routes was also reported. The used doses were 1ml/kg (Harish & Shivanandappa, 2006) 1.25 ml/Kg (Aktay et al., 2000) and 1.5 ml/kg (Gilani, & Janbaz, 1995). Subcutaneous route for administration of carbon tetrachloride was also used and the reported doses were 0.3 ml/kg (Kumar et al., 2009), 1 ml/kg (Ahmed et al., 2001) or 1.25 ml/kg (Mohamed et al., 2005).

3.1.2 Multi doses carbon tetrachloride-induced liver toxicity

The most popular multi-dose protocol for induction of liver toxicity is the subcutaneous administration of 2 ml of carbon tetrachloride/olive oil mixture (1:1) in days 2 and 3 of a five days long experiment (Zafar & Ali, 1998). In another protocol, carbon tetrachloride/olive oil (1:1) mixture was given daily via intraperitoneal injection in a 7 days long experiment. The doses were 0.5 ml (Maheswari & Rao, 2005), 0.8 ml (Özbek et al, 2004) or 1 ml/kg (Somasundaram et al., 2010). In 14 days experiment carbon tetrachloride/liquid paraffin mixture (1:1) was administered intraperitoneal every 72 hours (Christian et al., 2006). Chronic reversible cirrhosis were induced in rats by oral administration of mixture of 20% carbon tetrachloride in corn oil at 0.5mL/ kg body weight doses twice a week (Monday and Thursday) for 6 weeks (Hernandez-Munoz et al., 2001). Subcutaneous injection of 50% carbon tetrachloride in liquid paraffin (3 mL/kg) every other day for four weeks was also used to induce chronic liver toxicity (Chun-ching & Wei-Chih, 1995).

3.2 Paracetamol-induced liver toxicity

Paracetamol (acetaminophen) is a well-known antipyretic and analgesic agent. Therapeutic doses of paracetamol are safe, however, toxic doses can produce fatal hepatic necrosis in man, rats and mice (Mitchell et al., 1973). Paracetamol is eliminated mainly as sulfate and glucoronide (Eriksson et al., 1992) when administered in the regular therapeutic doses. Only 5% of the dose is converted into *N*-acetyl-*p*-benzoquineimine (NAPQI). However, upon administration of toxic doses of paracetamol the sulfation and glucoronidation routes become saturated and hence, higher percentage of paracetamol molecules are oxidized to highly reactive NAPQI by cytochrome p-450 enzymes. Semiquinone radicals, obtained by one electron reduction of NAPQI, has an extremely short half-life and is rapidly conjugated with glutathione (GSH), a sulphydryl donor which results in the depletion of liver GSH pool (Remirez et al., 1995). Under conditions of excessive NAPQI formation or reduced of glutathione store, NAPQI covalently binds to vital proteins, the lipid bilayer of hepatocyte membranes and increases the lipid peroxidation. The result is hepatocellular death and centrilobular liver necrosis (McConnachie et al., 2007). Due to liver injury caused by paracetamol overdose, the transport function of the hepatocytes gets disturbed resulting in leakage of plasma membrane (Zimmerman & Seeff, 1970), thus causing an increase in serum enzyme levels.

When rats are used as experimental animal model a single oral dose of 2 gm/kg paracetamol was used to induce liver damage (Chattopadhyay, 2003). The dose in case of using mice was 250 mg/kg (Sabir & Rocha, 2008). Intraperitoneal route of administration was also utilized. A doses of 750 mg/kg (Bhakta et al., 2001) or 835 mg/kg (Yen et al., 2007) were administered to produce liver intoxication in rats, while lower doses of 300 mg/kg (Yuan et al., 2010) were used for induction of liver damage in mice.

3.3 D-Galactosamine-induced liver toxicity

Exogenous administration of D-galactosamine (D-GalN) has been found to induce liver damage closely resembles human viral hepatitis (Decker & Keppler, 1972). A single injection of D-GalN can decrease the uracil nucleotides in the liver and heart (Wills & Asha, 2006). D-GalN markedly depletes hepatic UDP-glucuronic acid whereas extrahepatic UDP-glucuronic is minimally affected. This suggests that D-GalN predominantly inhibits hepatic glucuronidation. It disrupts the synthesis of essential uridylate nucleotides resulting in organelle injury. Depletion of these nucleotides ultimately impairs the synthesis of protein and glycoprotein, leads to progressive damage of cellular membranes. These consequences lead to change in cellular membrane permeability which leads to enzyme leakage to the circulation (Keppler et al., 1970; Abdul-Hussain & Mehendale, 1991). In addition, increased production of reactive oxygen species (ROS) has been reported in primary culture of rat hepatocytes treated with D-GalN (Quintero et al., 2002). Oxygen-derived free radicals released from activated hepatic-macrophages are also one of the primary causes of D-GalN-induced liver damage (Shiratori et al., 1988; Hu & Chen, 1992).

Experimentally induced liver damage was achieved in rats by a single dose of D-GalN 400 mg/kg (Ferenčiková et al., 2003; Kmieć et al., 2000) or 200 mg/kg (Decker & Keppler, 1974) via intrapretoneal injection. For induction of liver toxicity in mice a single dose of 15 mg D-GalN in 0.3mL saline per 20 g by intraperitoneal injection (Wang et al., 2000) was used. The use of D-GalN as liver toxin with a very small concentration of lipopolysaccharide (LPS) (10 μg/kg) was also reported (Tiegs et al., 1989).

3.4 Other methods for induction of hepatotoxicity

These methods include the use of some drugs with known side effects target the liver upon prolonged use. Rifampicin (1 g/kg in rats) (Anusuya et al., 1010), menadione (60 mg/kg in mice) (Ip et al., 2004) and anti-tubercular drugs were applied for induction of experimental liver toxicity (Tandon et al., 2008). Ethanol induced liver damage is a major cause of morbidity and mortality worldwide (Purohit et al., 2009). Consequently, ethanol was used as a liver damaging agent in some experiments (Noh et al., 2011; Sathaye et al., 2010). Natural toxins such as aflatoxins are known to have toxic effect on liver. Aflatoxin B1, under the influence of microsomal cytochrome p-450 mediated oxidation, is biotransformed into aflatoxin 8-9-epoxide, which is a reactive intermediate and highly toxic (Iyer et al., 1994). The use of aflatoxin B1 and other aflatoxins as hepatotoxic agent in experimental animal was reported (Banu et al., 2009; Naaz et al., 2007). Chemicals such as trichloroacetic acid (Celik et al., 2009), nitrobenzene (Rathi et al, 2010), thioacetamide (Khatri et al, 2009) and heavy metals such as Cadmium (Obioha et al., 2009) were also utilized to induce experimental liver injury.

Away from the use of chemicals, the hepatoprotective effect of some plant extracts was challenged against liver fibrosis caused by bile duct ligation (Fursule & Patil, 2010).

4. Assement of hepatoprotective activity

The experimental animals are usually treated with the plant extract under investigation for specified period of time. The hepatotoxic agent is usually administered near the end of the experimental period for induction of acute toxicity or in several doses during the course of the experiment for chronic toxicity. The hepatoprotective power of the tested material is assessed by measuring certain biochemical parameters, liver tissue parameters and comparing their levels with normal animals, group receiving standard drug in addition to the hepatotoxic agent and group receiving only hepatotoxic agent. The most common measured parameters are summarized below.

4.1 Serum biochemical parameters

4.1.1 Transaminases

Alanine transaminase (ALT), also called Serum Glutamic Pyruvate Transaminase (SGPT) or Alanine aminotransferase (ALAT) is an enzyme present in hepatocytes. Upon cell damaged, the enzyme leaks into the blood. SGPT level rises dramatically in acute liver damage, such as viral hepatitis or paracetamol overdose (Zimmerman & Seeff, 1970). Elevations are often measured in multiples of the upper limit of normal values. Aspartate transaminase (AST) also called Serum Glutamic Oxaloacetic Transaminase (SGOT) or aspartate aminotransferase (ASAT) is another enzyme associated with liver parenchymal cells. The level of SGOT is raised in acute liver damage, however, it is not specific as it is also present in red blood cells, heart, kidney and skeletal muscle. The ratio of SGOT to SGPT is sometimes useful in differentiating between liver damage and other conditions that elevate the levels of transaminases (Nyblom et al., 2004; Feild et al., 2008). Effective hepatoprotective agents must decrease the elevated levels of transaminases and bring them closer to the normal values as a signe for liver healing.

4.1.2 Alkaline phosphatase

Alkaline phosphatase (ALP) catalysis the hydrolysis of phosphate esters, and is found in biliary epithelium and the bile canalicular region of hepatocytes. Its function is not well established, but is thought to involve in metabolite transport across cell membranes. Elevation of the level of ALP can suggest intrahepatic, extrahepatic biliary obstruction, or infiltrative diseases of the liver (Feild et al., 2008). Agents that can lower ALP levels will be considered as useful hepatoprotective agents.

4.1.3 Bilirubin

Bilirubin (Bil) is the breakdown product of normal haem -a part of haemoglobin in red blood cells- catabolism of aged erythrocytes. Bilirubin, loosely bound to albumin in plasma to form a soluble species taken up from the Disse spaces of liver sinusoids into hepatocytes, where it is esterified at its propionyl sites with glucuronic acid under the catalytic activity of uridinediphosphoglucuronate 1A1 transferase enzymes. Esterified bilirubin is excreted into bile as water-soluble bilirubin diglucuronide. Serum concentration of bilirubin is a marker of the liver's ability to take up bilirubin from the plasma into the hepatocyte, conjugate it with glucuronic acid, and excrete bilirubin glucuronides into bile. Elevated level of serum conjugated bilirubin implies regurgitation of bilirubin glucuronides from hepatocytes back into plasma, usually because of intrahepatic or extrahepatic obstruction to bile outflow and cholestasis. The liver has substantial reserve capacity, and normal serum bilirubin levels can be maintained until there is enough injury to reduce the liver's capacity to clear bilirubin from plasma. Serum concentration of bilirubin is very specific for potentially serious liver damage, and is an important indicator of the loss of liver function (Feild et al., 2008). Reduction in the level of serum bilirubin is a strong indication of restoring normal liver function.

4.1.4 Gamma glutamyl transpeptidase (GGT)

Serum Gamma glutamyl transpeptidase (GGT) (also Gamma-glutamyl transferase) is specific to liver injury and more sensitive marker for cholestatic damage than ALP. GGT may be elevated with even minor, sub-clinical levels of liver dysfunction. GGT is raised in alcohol toxicity following several days of moderate ingestion. Rifampin, phenytoin, or barbiturates all resulted in elevation of GGT level. An isolated GGT elevation in these situations does not indicate hepatocellular injury. The GGT level will return to normal after discontinuation of the offending agent. Hepatic dysfunction should be considered if the GGT elevation is associated with other abnormalities in liver biochemistry (Owvens& Evans, 1975). Hepatoprotective agents will reduce the elevated level of GGT.

4.1.5 Total protein & albumin (Alb)

One of the most important liver functions is protein synthesis. Albumin is a major part of the total protein (TP) made specifically by the liver. Liver damage causes disruption and disassociation of polyribosomes on endoplasmic reticulum and thereby reducing the biosynthesis of protein. The TP levels including Alb levels will be depressed in hepatotoxic conditions due to defective protein biosynthesis in liver. Restoring the normal levels of TP including Alb is an important parameter for liver recovery (Navarro & Senior, 2006).

4.2 Liver tissue parameters

4.2.1 Glutathione and antioxidant enzymes

Glutathione (GSH) and its related enzymes are playing a vital role as intracellular antioxidants. GSH prevents damage to important cellular components caused by reactive oxygen species such as free radicals and peroxides (Pompella et al., 2003). Glutathione exists in both reduced (GSH) and oxidized (GSSG) states as well. In the reduced state, the thiol group of cysteine is able to donate a reducing equivalent (H^{+}+ e^{-}) to other unstable molecules, such as ROS. In donating an electron, GSH itself becomes reactive, but readily reacts with another reactive GSH to form glutathione disulfide (GSSG). Such a reaction is possible due to the relatively high concentration of glutathione in cells (up to 5 mM in the liver). GSH can be regenerated from GSSG by the enzyme glutathione reductase (GSR or GR) (Boyer, 1989; Tandogan & Ulusu, 2006). In healthy cells and tissues, more than 90% of the total glutathione pool is in the reduced form (GSH) and less than 10% exists in the disulfide form (GSSG). An increased GSSG-to-GSH ratio is considered indicative of oxidative stress (Pastore et al., 2003). Another protection from oxidative damage is assured by Glutathione peroxidase (GPx), an enzyme family with peroxidase activity. GPx reduce lipid hydroperoxides to their corresponding alcohols and breakdown hydrogen peroxide into water and oxygen (Castro & Freeman, 2001).

The glutathione *S*-transferase (GSTs) family are composed of many cytosolic, mitochondrial, and microsomal proteins. GSTs catalyze a variety of reactions and accept endogenous and xenobiotic substrates as well (Udomsinprasert et al., 2005). GSTs catalyse the conjugation of reduced glutathione - via a sulfhydryl group - to electrophilic centres on a wide variety of substrates (Douglas, 1987). This activity detoxifies endogenous compounds such as peroxidised lipids, and enable the breakdown of xenobiotics. GSTs may also bind toxins and serve as transport proteins (Leaver & George, 1998).

Plant	Dose	SGOT		SGPT		ALP		T.Bil		Ref.
		Test	St	Test	St	Test	St	Test	St	
Abutilon indicum	200	64.6	81.5	69.2	90.5	46.9	62.7	54.6	73.8	Porchezhian & Ansari, 2005
Abutilon indicum [a]	200	32.7	68.5	78.8	83.8	52.3	72.4	60.7	70.8	Porchezhian & Ansari, 2005
Adhatoda vasica	100	53.3	62.8	56.0	59.4	-	-	-	-	Bhattacharyya et al., 2005
Anisochilus carnosus	400	52.8	54.9	29.9	30.1	28.2	28.7	13.2	10.5	Venkatesh et al., 2011
Arachniodes exilis	750	71.9	75.8	41.7	49.3	-	-	-	-	Zhou et al., 2010
Artemisia absinthium	200	64.7	70.9	60.1	61.4	-	-	-	-	Amat et al., 2010
Azadirachta indica [a]	500	30.6	36.4	26.9	59.0	28.0	45.5	40.4	53.6	Gomase et al., 2011
Balanites aegyptiaca	500	28.7	56.9	29.9	64.5	21.5	42.8	38.4	52.0	Abdel-Kader & Alqasoumi, 2008
Bixa orellana	500	57.37	-	52.08	-	-	-	21.15	-	Ahsan et al., 2009
Butea monosperma	800	52.1	53.2	78.1	87.1	-	-	-	-	Sharma & Shukla, 2010
*Byrsocarpus coccineus**	400	44.3	42.9	68.4	55.9	49.0	38.5	46.6	51.0	Akindele et al., 2010
Cajanus cajan	500	56.53	-	50.22	-	-	-	25.0	-	Akindele et al., 2010
Calotropis procera [a]	400	62.2	66.5	69.1	73.5	58.4	61.9	68.7	69.6	Setty et al., 2007
Cassia fistula [a], **	400	54.0	64.3	46.4	63.1	53.9	58.2	54.1	66.5	Bhakta et al., 2001
Castanea crenata [c]	150	54.1	-	70.6	-	-	-	-	-	Noh et al., 2011
Carduus nutans	500	44.16	-	64.68	-	-	-	-	-	Aktay et al., 2000
Chamomile capitula [a]	400	-	-	-	-	82.6		74.2	-	Gupta & Misra, 2006
Cichorium intybus	500	81.9	78.1	56.1	84.3	40.8	47.3	-	-	Ahmed et al., 2003
Cistanche tubulosa	1000	91.6	-	89.7	-	-	-	-	-	Morikawa et al., 2010
Clerodendrum inerme	200	31.6	40.1	83.0	85.6	88.4	89.0	-	-	Gopal & Sengottuvelu, 2008
Commiphora berryi	200	45.6	44.4	65.8	62.4	61.1	65.7	56.3	73.6	Shankar et al., 2008
C. opobalsamum	500	66.2	-	75.6	-	33.0	-	37.3	-	Al-Howiriny et al., 2004
Coptidis rhizoma	600	93.9	-	82.5	-	-	-	-	-	Ye et al., 2009
Cordia macleodii	200	84.8	86.5	77.5	82.2	63.3	60.6	40.6	42.2	Qureshi et al., 2009
Cuscuta chinensis [a]	250	86.8	-	81.6	-	31.0	-	-	-	Yen et al., 2007
Enicostemma axillare [b]	200	91.1	92.2	45.3	20.4	49.2	40.3	33.3	18.6	Jaishree & Badami, 2010
Ephedra foliata	500	42.6	55.1	39.5	66.1	21.2	39.6	46.2	63.5	Alqasoumi et al., 2008b
Euphorbia fusiformis	500	43.1	43.7	30.2	31.7	34.7	37.1	99.9	65.9	Anusuya et al., 2010
Ficus glomerata	500	44.0	30.4	72.8	57.2	68.5	74.6	-	-	Channabasavaraj et al., 2008
Filipendula ulmaria	100	58.7	-	81.9	-	-	-	-	-	Shilova et al., 2008
Fumaria indica [b]	400	72.6	-	79.0	-	68.2	-	79.7	-	Rathi et al., 2008
F. vailantii	500	60.75	-	66.93	-	-	-	-	-	Aktay et al., 2000
Ganoderma lucidum [b]	180	76.6	-	83.6	-	-	-	-	-	Shi et al., 2008
Gentiana olivieri	500	69.57	-	86.39	-	-	-	-	-	Aktay et al., 2000
Hibiscus sabdariffa	500	44.5	66.5	37.1	65.02	21.0	50.6	35.0	69.6	Alqasoumi et al., 2008b
Halenia elliptica	200	57.2	48.8	58.0	47.6	39.0	49.4	46.6	48.6	Huang et al., 2010b
Hedyotis corymbosa [a]	200	59.6	60.8	75.8	66.9	81.0	79.2	37.8	72.4	Sadasivan et al., 2006
Helminthostachys zeylanica	300	64.3	65.0	77.7	78.2	44.3	45.1	66.4	74.0	Suja et al., 2004
Hygrophila auriculata	150	40.8	43.2	24.9	23.5	28.1	26.2	53.0	60.2	Shanmugasundara & Venkataraman, 2006
Kyllinga nemoralis	200	45.6	42.5	68.3	65.5	61.3	66.0	46.6	51.1	Somasundaram et al., 2010
Laggera pterodonta	100	39.6	7.3	31.3	12.5	-	-	-	-	Wu et al., 2007
Laggera pterodonta [b,***]	100	41.9	9.3	35.0	7.5	-	-	-	-	Wu et al., 2007
Mollugo pentaphylla	200	37.2	43.6	53.0	63.9	55.1	55.6	32.6	36.0	Valarmathi et al., 2010
Momordica balsamina	500	37.5	57.6	39.1	57.1	23.2	37.5	52.7	62.0	Alqasoumi et al., 2009b
M. dioica	200	44.7	64.0	54.3	54.6	51.9	59.7	31.1	58.5	Jain et al., 2008
Nelumbo nucifera	500	82.8	82.0	76.5	74.3	39.7	42.0	46.5	50.5	Huang et al., 2010a
Phyllanthus amarus [d]	75	16.6	21.9	28.1	31.8	-	-	-	-	Pramyothin, et al., 2007
Pittosporum neelgherrense	200	70.6	71.9	54.1	55.5	-	-	-	-	Shyamal et al., 2006
Pittosporum neelgherrense[b]	200	65.5	65.4	58.4	59.1	-	-	-	-	Shyamal et al., 2006
Propolis	500	29.4	53.4	37.3	60.2	25.5	43.5	30.1	57.0	Alqasoumi et al., 2008a
Premna corymbosa	400	-	-	-	-	61.6	52.4	-	-	Karthikeyan & Deepa, 2010
Rubus aleaefolius	35	12.7	-	-	-	-	-	-	-	Hong et al., 2010
Sida acuta [a]	100	61.9	60.7	67.7	66.9	79.6	79.2	67.3	72.4	Sreedevi et al., 2009
Smilax regelii	500	13.5	-	47.0	-	-	-	56.4	-	Rafatullah et al., 1991

[a] Paracetamol, [b] D-galactosamine, [c] ethanol, [d] aflatoxin, [e] nitrobenzene, [f] thioacetamide- induced liver toxicity, otherwise CCl_4 was used

* Livolin, ** Liver tonic, *** Silibinin were used as hepatoprotective standard, otherwise silymarin was use

Table 1. Effect of selected plants on serum biochemical parameters

Treatment of animals with hepatotoxic agents lead to depletion of GSH, reduction in the non-protein sulfhydryl moiety (NP-SH), GPx, GSR activities and ultration of GSTs activity (Naaz et al., 2007; Mitchell et al., 1973; Abdel-Kader et al., 2010; Alqasoumi et al., 2009).

Another part of the antioxidant systems in the bodies is the enzymes Superoxide dismutases (SOD) and Catalase (CAT) (Scott et al., 1991). They are an important antioxidant defence containing heavy metals in nearly all cells exposed to oxygen. SOD catalyzes the dismutation of superoxide into oxygen and hydrogen peroxide. SOD is the most efficient catalytic enzyme; its activity is only limited by the frequency of collision between itself and superoxide (Fredovich, 1997).

CAT catalyzes the decomposition of hydrogen peroxide to water and oxygen (Chelikani et al., 2004). CAT has one of the highest turnover numbers of all enzymes; one CAT enzyme can convert 40 million molecules of hydrogen peroxide to water and oxygen per second (RCSB Protein Data Bank, 2007).

Effective hepatoprotactive agents will be able to restore the normal levels of these systems in liver tissue.

4.2.2 Harmful peroxidation products

Malonaldehyde (MDA) is the main end-product of polyunsaturated fatty acid peroxidation (PUFA) following Reactive oxygen species (ROS) insult (Esterbauer et al., 1991). PUFA are essential part of biological membranes (Vaca et al., 1988). MDA is a reactive aldehyde and is one of many reactive electrophile species that cause toxic stress in cells and form covalent protein adducts (Farmer & Davoine, 2007). The production of this aldehyde is used as a biomarker to measure the level of oxidative stress in an organism (Del Rio et al., 2005). The increase in liver MDA levels induced by hepatotoxic agents suggests enhanced lipid peroxidation, leading to hepatic tissue damage and failure of endogenous antioxidant defence mechanisms to prevent formation of excessive free radicals (Souza et al., 1997).

ThioBarbituric Acid Reactive Substances (TBARS) are another harmful substances formed by lipid peroxidation. TBARS are one of the end products formed during the decomposition of lipids by ROS (Olinescu et al., 1994). The tissue concentration of TBARS increase with induced liver toxicity (Sabir & Rocha, 2008).

Physiological amounts of nitric oxide (NO) in the liver has protective effect against damage induced by tumour necrosis factor-a or Fas-dependent apoptosis (Fiorucci et al., 2001). The production of high levels of NO within the liver, via inducible NO synthase (iNOS) promote damage via interference with mitochondrial respiration (Moncada & Erusalimsky, 2002). Hepatocytes of experimental animals produce NO during chronic hepatic inflammation (Billiar et al., 1990 a, b). Human hepatocytes were also stimulated to produce NO by the same combination of endotoxin and cytokines as rat hepatocytes (Palmer et al., 1988; Nussler et al., 1992).

ROS are known to convert amino groups of protein to carbonyl moieties (Perry et al. 2000). Oxidative modification of protein leads to increased recognition and degradation by proteases and loss of enzymatic activity (Rivett & Levine, 1990). Accumulation of carbonyl derivatives of proteins (protein carbonyl) is taken as a biomarker of oxidative protein damage in aging and in various diseases (Dalle-Donne et al., 2003).

Plant	Dose	SOD		CAT		GSH		GPx		MDA		TBAR	
Abutilon indicum	200	-	-	-	-	81.4	82.8	-	-	-	-	-	
Abutilon indicum [a]	200	-	-	-	-	75.9	77.3	-	-	-	-	-	
Adhatoda vasica	100	-	-	-	-	-	-	-	-	-	-	55.4	5
Arachniodes exilis	750	88.4	91.4	-	-	-	-	-	-	50.0	55.4	-	
Artemisia absinthium	200	88.0	90.1	-	-	-	-	71.7	89.0	54.9	58.6	-	
Butea monosperma	800	-	-	-	-	92.3	92.3	-	-	-	-	-	
Byrsocarpus coccineus *	400	92.8	73.6	93.7	73.6	104.5	75.5	92.2	96.0	82.7	87.3	-	
Calotropis procera [a]	400	-	-	-	-	58.4	60.5	-	-	-	-	-	
Castanea crenata [c]	150	104.8	-	89.0	-	-	-	38.6	-	-	-	21.8	
Carduus nutans	500	-	-	-	-	-	-	-	-	34.8	-	-	
Chamomile capitula [a]	400	-	-	-	-	91.0	-	-	-	-	-	50.2	
Clerodendrum inerme	200	-	-	-	-	92.9	88.2	-	-	-	-	-	
C. opobalsamum	500	-	-	-	-	92.6	-	-	-	-	-	-	
Coptidis rhizoma	600	97.5	-	-	-	-	-	-	-	-	-	-	
Cuscuta chinensis [a]	250	87.4	-	86.6	-	-	-	95.6	-	55.4	-	-	
Ficus glomerata	500	62.5	106.3	105.0	101.7	-	-	-	-	-	-	44.1	4
Filipendula ulmaria	100	66.0	56.1	92.9	73.2	-	-	-	-	-	-	48.4	3
Fumaria indica [b]	400	-	-	-	-	-	-	89.8	93.2	48.6	55.1	-	
F. vailantii	500	-	-	-	-	-	-	-	-	33.7	-	-	
Ganoderma lucidum [b]	180	98.5	-	-	-	96.1	-	-	-	51.6	-	-	
Gentiana olivieri	500	-	-	-	-	-	-	-	-	32.3	-	-	
Kyllinga nemoralis	200	66.1	51.4	81.3	87.3	59.0	57.2	-	-	51.1	52.6	-	
Memordica dioica	200	76.8	84.5	83.0	91.5	85.3	88.0	-	-	36.0	48.8	-	
Nelumbo nucifera	500	85.4	76.5	87.9	55.7	126.0	78.7	-	-	-	-	31.0	3
Phyllanthus amarus [d]	75	85.4	-	100.1	-	202.3	-	108.0	-	-	-	48.3	
Rubus aleaefolius	35	89.8	-	-	-	-	-	-	-	20.1	-	-	
Tecomella undulata [e]	1000	-	-	-	-	134.9	150.9	-	-	50.7	69.4	-	
Tephrosia purpurea [e]	500	-	-	-	-	139.0	150.9	-	-	65.0	69.4	-	
Trichosanthes cucumerina	500	-	-	-	-	93.8	94.9	-	-	51.2	54.4	-	
Spermacoce hispida	200	85.1	-	82.9	-	-	-	89.9	-	51.7	-	-	
Uvaria chamae [a]	60	-	-	-	-	-	-	-	-	-	-	-	
Zanthoxylum armatum	400	93.7	99.7	90.9	97.9	89.0	94.2	-	-	67.3	70.0	-	

[a] Paracetamol, [b] D-galactosamine, [c] ethanol, [d] aflatoxin, [e] thioacetamide- induced liver toxicity, otherwise CCl_4 wa
* Livolin was used as hepatoprotective standard, otherwise silymarin was use

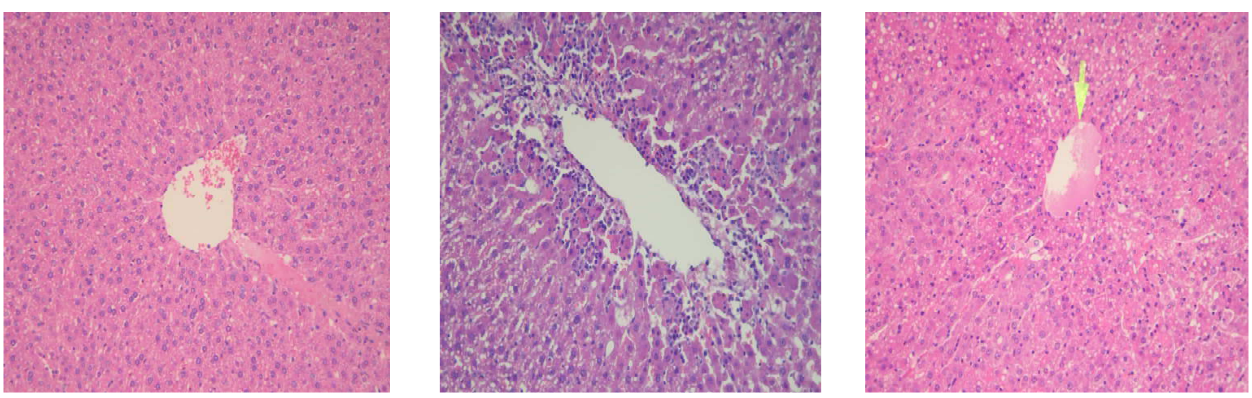
Table 2. Effect of selected plants on liver tissue parameters

4.3 Barbiturates sleep time

Short acting barbiturates such as hexobarbiton are metabolized almost exclusively in the liver. Duration of barbiturates induced sleep in intact animals is considered as a reliable index for the activity of hepatic metabolism (Vogel, 1977). Pre-existing liver damage will result in prolongation of the sleeping time after a given dose of barbiturates due to decrease in the amount of the hypnotic broken down per unit time as a result of decreased availability of CYP2E1 contents (Singh et al., 2001). Extracts that can shorten this prolongation of barbiturates sleep time exert protective effect on CYP2E1 system.

4.4 Histopathological study of liver tissue

The histological appearance of the hepatocytes reflects their damage conditions (Prophet, et al., 1994). Exposure of hepatocytes to toxic agents such as carbon tetrachloride leads to histopathological changes from the normal histological appearance (Fig. 1). The hepatocytes of rat treated with carbon tetrachloride, showed centrilobular necrosis and extensive fatty changes observed on the midzonal or entire lobe 24 h after treatment (Fig. 1B). Liver tissues of rats treated with carbon tetrachloride and the standard drugs like silymarin showed no necrosis or fatty deposition but had only minimal portal inflammation (Fig.1C). The protective effect of tested extracts or pure materials will be expressed in histopathology as the ability to improve the histological appearance of hepatocytes and bring it closer to the normal hepatocytes of healthy liver (Fig.1A).



1A **1B** **1C**

Fig. 1. Histological appearance of normal liver (1A), rat liver treated with carbon tetrachloride (1B), rat liver treated with silymarin+ carbon tetrachloride (1C)(H & E, ×200).

5. Literature results for some promising hepatoprotective plants

Many plant extracts were tested for their hepatoprotective activity against various liver toxins. All the above mentioned parameters were used to evaluate the protective power of such plants against liver cells damage. In the following Tables some of the most promising results are presented. For handy comparative evaluation of the results percentage of protection is presented even if it was not calculate in the original article. For values where normal levels are increase due to destruction of hepatocytes integrity (SGOT, SGEPT) or over production of harmful oxidation products (MDA, TBARS) calculations were preformed based on control groups receiving the hepatotoxic agents. Percentage of reduction in the elevated values was compared to protection achieved by silymarin or any other hepatoprotective agents used in the original articles. On the other hand when experimental liver toxicity resulted in decrease in the normal levels of the measured parameters like the case of normal protective antioxidant enzymes (SOD, CAT), the protection efficacy is presented as percent recovery relative to the negative control values.

6. Summary, conclusions and future directions

Liver diseases represent a major global health problem that still has no cure in modern medicine. Some of the traditionally used plants for liver disorders provided useful therapeutic agents. A large number of such plants lack the scientific evidences supporting their effectiveness. Many groups of researchers worldwide were involved in studying the protective effects of plant extracts against experimentally induced liver toxicity. Rats and mice are the animals of choice in such experiments. Carbon tetrachloride followed by paracetamol and D-galactosamine (D-GalN) were used to induce liver toxicity in addition to ethanol and some other drugs affecting the liver on prolonged use. In most cases, positive control groups received silymarin as standard drug for liver protection. Both serum biochemical parameters, liver tissue parameters, barbiturates sleeping time and histopathological examination were used to access liver protection. The most promising data were presented in tables 1 and 2. These biological studies are extremely important to discriminate between useful and useless plants claimed to have liver healing properties. Scientific examination of all traditionally used plants for liver problems is a great goal still to be achieved. This collection of data can be a helpful guide for Phytochemists to explore the constituents of the most promising plants in order to discover new useful natural drugs for the management of liver disorders.

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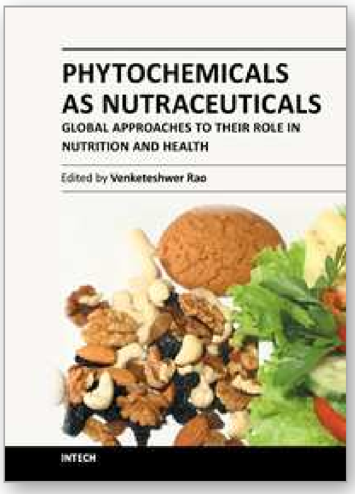

Phytochemicals as Nutraceuticals - Global Approaches to Their Role in Nutrition and Health

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Phytochemicals are biologically active compounds present in plants used for food and medicine. A great deal of interest has been generated recently in the isolation, characterization and biological activity of these phytochemicals. This book is in response to the need for more current and global scope of phytochemicals. It contains chapters written by internationally recognized authors. The topics covered in the book range from their occurrence, chemical and physical characteristics, analytical procedures, biological activity, safety and industrial applications. The book has been planned to meet the needs of the researchers, health professionals, government regulatory agencies and industries. This book will serve as a standard reference book in this important and fast growing area of phytochemicals, human nutrition and health.