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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).

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| 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

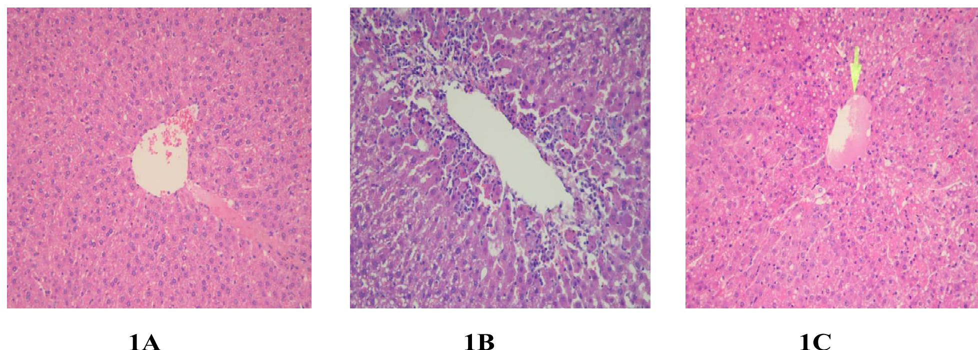
Table 2. Effect of selected plants on liver tissue parameters

### 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.

## 7. Reference

Abdel-Kader, M. S. & Alqasoumi, S. I. (2008). Evaluation of the hepatoprotective effect of the ethanol extracts of *Solanum nigrum*, *Cassia fistula*, *Balanites aegyptiaca* and *Carthamus tinctorius* against experimentally induced liver Injury in Rats. *Alexandria Journal of Pharmaceutical Sciences*, Vol 22, No.1, pp. 47- 50, ISSN 1110-1792

Abdel-Kader, M. S.; Alqasoumi, S. I.; Hefnawy, M. M. & AlSheikh, A. M. (2010). Hepatoprotective effect and safety studies of *Cleome droserifolia*. *Alexandria Journal of Pharmaceutical Sciences*, Vol 24, No.1, pp. 13- 21, ISSN 1110-1792

Abdul-Hussain, S. K. & Mehendale, H. M. (1991). Studies on the age dependant effect of galactosamine in primary rat hepatocyte cultures. *Toxicology and Applied Pharmacology*, Vol 107, pp. 504–513, ISSN 0041-008X

Al-Howiriny, T. A.; Al-Sohaibani, M. O.; Al-Said, M. S.; Al-Yahya, M. A.; El-Tahir, K. H. & Rafatullah, S. (2004). Hepatoprotective properties of *Commiphora opobalsamum* (Balessan, A traditional medicinal plant of Saudi Arabia. *Drugs Under Experimental & Clinical Research*, Vol XXX, No.5/6, pp. 213- 220, ISSN 0378-6501

Ahmed, B.; Alam, T. & Khan, S. A.(2001). Hepatoprotective activity of *Luffa echinata* fruits. *Journal of Ethnopharmacology*, Vol 76, No.2 ,pp. 187–189, ISSN 0378-8741

Ahmed, B.; Al-Howiriny, T. A. & Siddiqui, A. B. (2003). Antihepatotoxic activity of seeds of *Cichorium intybus*. *Journal of Ethnopharmacology*, Vol 87, No. 2-3, pp. 237-240, ISSN 0378-8741

Ahsan, R., Islam, K. M.; Musaddik, A. & Haque, E. (2009). Hepatoprotective activity of methanol extract of some medicinal plants against carbon tetrachloride induced hepatotoxicity in albino rats. *Global Journal of Pharmacology*, Vol 3, No.3, pp. 116-122, ISSN 1992-0075

Akindele; A. J.; Ezenwanebe, K. O.; Anunobi, C. C. & Adeyemi, O. O. (2010). Hepatoprotective and in *vivo* antioxidant effects of *Byrsocarpus coccineus* Schum. and Thonn. (Connaraceae). *Journal of Ethnopharmacology*, Vol 129, No.1, pp. 46-52, ISSN 0378-8741

Aktay, G., Deliorman, D.; Ergun, E.; Ergun, F.; Yeşilada, E. & Cęvik, C. (2000). Hepatoprotective effects of Turkish folk remedies on experimental liver injury. *Journal of Ethnopharmacology*, Vol 73, pp. 121–129, ISSN 0378-8741

Alqasoumi, S. I.; El Tahir, K. E. H.; AlSheikh, A. M. & Abdel-Kader, M. S. (2009a). Hepatoprotective Effect and Safety Studies of *Juniperus phoenicea*. *Alexandria Journal of Pharmaceutical Sciences*, Vol 23, No.2, pp. 81- 88, ISSN 1110-1792

Alqasoumi, S. I.; Al-Howiriny, T. A. & Abdel-Kader, M. S. (2008a). Evaluation of the hepatoprotective effect of *Aloe Vera, Clematis hirsute, Cucumis prophetarum* and Bee Propolis against experimentally induced liver injury in rats. *International Journal of Pharmacology*, Vol 4, No.3, pp. 213- 217, ISSN 1811-7775

Alqasoumi, S. I.; Al-Dosari, M. S.; AlSheikh, A. M. & Abdel-Kader, M. S. (2009b). Evaluation of the hepatoprotective effect of *Fumaria parviflora* and *Momordica balsamina* from Saudi Folk medicine against experimentally induced liver injury in rats. *Research Journal of Medicinal Plant*, Vol 3, No.1, pp. 9- 15, ISSN 1996-0875

Alqasoumi, S. I.; Al-Rehaily, A. J.; Abdulmalik M. AlSheikh & Abdel-Kader, M. S. (2008b). Evaluation of the hepatoprotective effect of *Ephedra foliate*, *Alhagi maurorum*, *Capsella bursa-pastoris* and *Hibiscus sabdariffa* against experimentally induced liver injury in rats. *Natural Product Sciences*, Vol 14, No.2, pp. 95-99, ISSN 1226-3907

Amat, N.; Upur, H. & Blažeković, B. (2010). *In vivo* hepatoprotective activity of the aqueous extract of *Artemisia absinthium* L. against chemically and immunologically induced liver injuries in mice. *Journal of Ethnopharmacology*, Vol 131, No.2, pp. 478–484, ISSN 0378-8741

Anusuya, N.; Raju, K. & Manian, S. (2010). Hepatoprotective and toxicological assessment of an ethnomedicinal plant *Euphorbia fusiformis* Buch.-Ham.ex D.Don. *Journal of Ethnopharmacology*, Vol 127, No.2, pp. 463–467, ISSN 0378-8741

Azri, S.; Mat, H. P.; Reid, L. L.; Gandlofi, A. J. & Brendel, K. (1992). Further examination of the selective toxicity of CCl4 rat liver silices. *Toxicology and Aplied Pharmacology*, Vol 112, No.1, pp. 81- 86, ISSN 0041-008X

Banu, G. S.; Kumar, G. & Murugesan, A. G. (2009). Effect of ethanolic leaf extract of *Trianthema portulacastrum* L. on aflatoxin induced hepatic damage in rats. *Indian Journal of Clinical Biochemistry,* Vol 24, No.4, pp. 414-418, ISSN 0970-1915

Baranisrinivasan, P.; Elumalai, E. K.; Sivakumar, C.; Therasa, S. V. & David, E. (2009). Hepatoprotective effect of *Enicostemma littorale* blume and *Eclipta alba* during ethanol induced oxidative stress in albino rats. *International Journal of Pharmacology*, Vol 5, No.4, pp. 268–272, ISSN 1811-7775

Bhadauria, M.; Nirala, S. K.; Shrivastava, S.; Sharma, A.; Johri, S.; Chandan, B. K.; Singh, B.; Saxena, A. K. & Shukla, S. (2009). Emodin reverses CCl4 induced

hepaticcytochrome P450 (CYP) enzymatic and ultra structural changes: the *in vivo* evidence. *Hepatology Research*, Vol 39, No.3, 290-300, ISSN 1386-6346

Bhakta, T.; Banerjee, S.; Mandal, S. C.; Maity, T. K.; Saha, B. P. & Pal, M. (2001). Hepatoprotective activity of *Cassia fistula* leaf extract. *Phytomedicine*, Vol. 8, No.3, pp. 220–224, ISSN 0944-7113

Bhattacharyya, D.; Pandit, S.; Jana, U.; Sen, S. & Sur, T. S. (2005). Hepatoprotective activity of *Adhatoda vasica* aqueous leaf extract on d-galactosamine-induced liver damage in rats. *Fitoterapia*, Vol 76, No.2, 223– 225, ISSN 0367-326X

Billiar, T.R.; Curran, R. D.; Harbrecht, B. G.; Stuehr, D. J.; Demetris, A. J. & Simmons R. L. (1990a). Modulation of nitrogen oxide synthesis *in vivo*: NG-monomethyl-L-arginine inhibits endotoxin-induced nitrate/nitrite biosynthesis while promoting hepatic damage. *Journal of Leukocyte Biology,* Vol 48, No.6, pp. 568-569, ISSN 0741-5400

Billiar, T. R.; Curran, R. D.; Stuer, D. J.; Stadler, J.; Simmons, R. L. & Murray S. A. (1990b). Inducible cytosolic enzyme activity for the production of nitrogen oxide from L-arginine in hepatocytes. *Biochemical and Biophysical Research Communications*, Vol 168, No.3, pp. 1034-1040, ISSN 0006-291X

Boyer, T. D. (1989). The glutathione S-transferases: an update. *Hepatology,* Vol 9, No.3, pp. 486–496, ISSN 0270-9139

Castro, L. & Freeman, B. A. (2001). Reactive oxygen species in human health and disease. *Nutrition*, Vol 17, No.2, pp. 161–165, ISSN: 0899-9007

Celik, I.; Temur A. & Isik, I. (2009). Hepatoprotective role and antioxidant capacity of pomegranate (*Punica granatum*) flowers infusion against trichloroacetic acid-exposed in rats. *Food and Chemical Toxicology*, Vol 47, No.1, pp. 145–149, ISSN 0278-6915

Channabasavaraj, K. P.; Badami, S. & Bhojraj, S. (2008). Hepatoprotective and antioxidant activity of methanol extract of *Ficus glomerata*. *Journal of Natural Medicines*, Vol 62, No.3, pp. 379–383, ISSN 1340-3443

Chatterjee, T. K. (2000). *Medicinal Plants with Hepatoprotective Properties in Herbal Opinions*, Vol III. 135, Books and Allied (P) Ltd., Calcutta.

Chattopadhyay, R. R. (2003). Possible mechanism of hepatoprotective activity of *Azadirachta indica* leaf extract. Part II. *Journal of Ethnopharmacology*, Vol 89, No.2-3, pp. 217–219, ISSN 0378-8741

Chelikani, P.; Fita, I. & Loewen, P. C. (2004). Diversity of structures and properties among catalases. *Cellular and Molecular Life Sciences*, Vol 61, No.2, pp. 192–208, ISSN 1420-682X

Christian, A. J.; Saraswathy, G. R.; Robert, S. J.; Kothai, R.; Chidambaranathan, N.; Nalini, G. & Therasal R. L. (2006). Inhibition of CCl4 induced liver fibrosis by *Piper longum* Linn. *Phytomedicin*, Vol 13, pp. 196- 198, ISSN 0944-7113

Chun-Ching, L. & Wei-Chih, L. (1995). Anti-inflammatory and hepatoprotective effects of *Ventilago leiocarpa*. *Phytotherapy Research,* Vol 9, No.1, pp. 11-15. ISSN 0951-418X

Comoglio, A.; Leonarduzzi, G.; Carini, R.; Busolin, D.; Basaga, H.; Albano, E.; Tomasi, A.; Poli G.; Morazzoni, P. & Magistretti M. J. (1990). Studies on the antioxidant and free radical scavenging properties of IdB 1016: a new flavanolignan complex. *Free*

*Radical Research Communications*, Vol 11, No.1-3, pp. 109–115, Sons. ISSN 0951-418X

Cyong, J. C.; Ki, S. M.; Iijima, K.; Kobayashi, T. & Furuya, M. (2000). Clinical and pharmacological studies on liver diseases treated with kampo herbal medicine. *The American Journal of Chinese Medicine*, Vol 28, No.3-4, pp. 351–360, ISSN 0192-415X

Dalle-Donne, I.; Rossi, R.; Giustarini, D.; Aldo Milzani, A. & Colombo, R. (2003). Protein carbonyl groups as biomarkers of oxidative stress. *Clinica Chimica Acta*, Vol 329, No.1-2, pp. 23-38, ISSN 0009-8981

Decker, K. & Keppler, D. (1972). Galactosamine induced liver injury, In: *Progress in Liver Disease*, H. Popper; F., Schaffner (Eds.) 183–199, Grune and Stratton, New York.

Decker, K. & Keppler, D. (1974). Galactosamine hepatitis: key role of the nucleotide deficiency period in the pathogenesis of cell injury and cell death. *Reviews of Physiology, Biochemistry and Pharmacology,* Vol 71, pp. 77- 106, ISSN 0303-4240

Dehmlow, C.; Erhard, J. & de Groot, H. (1996). Inhibition of Kupffer cell functions as an explanation for the hepatoprotective properties of silibinin. *Hepatology*, Vol 23, No. 4, pp. 749–754, ISSN 0270-9139

Del Rio, D.; Stewart, A. J. & Pellegrini, N. (2005). A review of recent studies on malonaldehyde as toxic molecule and biological marker of oxidative stress. *Nutrition, Metabolism & Cardiovascular Diseases,* Vol 15, No.4, pp. 316 28, ISSN 0939-4753

Dianzani, M. U.; Muzia, G.; Biocca, M. E. & Canuto, R. A. (1991). Lipid peroxidation in fatty liver induced by caffeine in rats. *International Journal of Tissue Reaction*, Vol 13, No.1, pp. 79–85, ISSN 0250-0868

Douglas, K. T. (1987). Mechanism of action of glutathione-dependent enzymes. *Advances in Enzymology & Related Areas of Molecular Biology*, Vol 59, pp. 103–167, ISSN 0065258X

elSisi, A. E.; Earnest, D. L. & Sipes, I. G. (1993). Vitamin A potentiation of carbon tetrachloride hepatotoxicity: role of liver macrophages and active oxygen species. *Toxicology and Applied Pharmacology*, Vol 119, No.2, pp. 295–301, ISSN 0041-008X

Eriksson, L.; Broome, U., Kahn, M. & Lindholm, M. (1992). Hepatotoxicity due to repeated intake of low doses of paracetamol. *Journal of Internal Medicine*, Vol 231, No.5, pp. 567-570, ISSN 0041-008X

Esterbauer, H.; Schaur, R. J. & Zollner, H. (1991). Chemistry and biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. *Free Radical Biology and Medicine*, Vol 11, No.1, pp. 81–128, ISSN 0891-5849

Farmer, E. E. & Davoine, C. (2007). *Reactive electrophile species.* Current Opinion in Plant Biology, Vol 10, No.4, pp. 380- 386, *ISSN* 1369-5266

Ferenčiková, R.; Červinková, Z. & Drahota, Z. (2003). Hepatotoxic effect of D-galactosamine and protective role of lipid emulsion. *Physiological research*, Vol 52, No.1, pp. 73- 78, ISSN 0862-8408

Fiebrich, F. & Koch, H. (1979a). Silymarin, an inhibitor of lipoxygenase. *Experientia*, Vol 35, No.12, pp. 1548–1550, ISSN: 0014-4754

Fiebrich, F. & Koch, H. (1979b). Silymarin, an inhibitor of prostaglandin synthetase. *Experientia*, Vol 35, No.12, pp. 1550–1552, ISSN: 0014-4754

Field, K. M.; Dow, C. & Michael, M. (2008). Liver function in oncology: biochemistry and beyond. *The Lancet Oncolog*, Vol 9, No.11, pp. 1092–1101, ISSN 0140-6736

Fiorucci, S.; Mencarelli, A.; Palazzeti, B.; Del Soldato, P.; Morelli, A. & Ignarro, L.J. (2001). An NO-derivative of ursodeoxycholic acid protects against Fas-mediated liver injury by inhibiting caspase activity. *Proceedings of the National Academy of Sciences of the United States of America,* Vol 98, No.5, pp. 2652- 2657, ISSN 0027-8424

Fraschini, F.; Demartini, G. & Esposti, D. (2002). Pharmacology of silymarin. *Clinical Drug Investigation*, Vol 22, No.1, pp. 51–65, ISSN 1173-2563

Fredovich, I. (1997). Superoxide anion radical (O2-.), superoxide dismutases, and related matters. *The Journal of Biological Chemistry*, Vol 272, No.30, pp. 18515- 18517, ISSN 0021-9258

Fursule, R. A. & Patil, S. D. (2010). Hepatoprotective and antioxidant activity of Phaseolus trilobus, Ait on bile duct ligation induced liver fibrosis in rats. *Journal of Ethnopharmacology*, Vol 129, No.3 , pp. 416–419, ISSN 0378-8741

Gilani, A. H. & Janbaz, K. H. (1995). Preventive and curative effects of *Artemisia absinthium* on acetaminophen and CCl4-induced hepatotoxicity. *General Pharmacology,*Vol 26, No.2, pp. 309–315, ISSN 0306-3623

Gomase, P. V.; Rangari V. D. & Verma P. R. (2011). Phytochemical evaluation and hepatoprotective activity of fresh juice of young stem (tender) bark of *Azadirachta indica* A. JUSS. *International Journal of Pharmacy and Pharmaceutical Sciences*, Vol 3, Suppl 2, pp. 55- 59, ISSN 0975-1491

Gopal, N. & Sengottuvelu, S. (2008). Hepatoprotective activity of Clerodendrum inerme against CCL4 induced hepatic injury in rats. *Fitoterapia*, Vol 79, No.1, pp. 24– 26, ISSN 0367-326X

Gupta, A. K. & Misra, N. (2006). Hepatoprotective Activity of Aqueous Ethanolic Extract of *Chamomile capitula* in Paracetamol Intoxicated Albino Rats. *American Journal of Pharmacology and Toxicology*, Vol 1, No.1, pp. 17-20, ISSN 1557-4962

Hahn, G.; Lehmann, H. D.; Kurten, M.; Ubel, H. & Vogel, G. (1968). Zur Pharmakologie und Toxikologie von Silymarin, des antihepatotoxischen Wirkprinzipes aus *Silybum marianum* (L.) Gaertn. *Arzneimittelforschung*, Vol 18, pp. 698– 704, ISSN 0004-4172

Handa, S. S.; Sharma, A. & Chakarborti, K. K. (1986). Natural products and plants as liver protecting drugs. *Fitoterapia*, Vol 57, No.5, pp. 307–351, ISSN 0367-326X

Harish, R. & Shivanandappa T. (2006). Antioxidant activity and hepatoprotective potential of *Phyllanthus niruri*. *Food Chemistry*, Vol 95, No.2 ,pp. 180– 185, ISSN 0308-8146

Hernandez-Munoz, R.; Diaz-Munoz, M.; Suarez-Cuenca, J. A.; Trejo-Solis, C.; Lopez, V.; Sanchez-Sevilla, L.; Yanez, L. & De Sanches, V. C. (2001). Adenosine reverses a preestablished CCl4-induced micronodular cirrhosis through enhancing collagenolytic activity and stimulating hepatocyte cell proliferation in rats. *Hepatology*, Vol 34, No.4, pp. 677– 687, ISSN 0270-9139

Hong, Z.; Chen, W.; Zhao, J.; Wu, Z.; Zhou, J. H.; Li, T. & Hu J. (2010). Hepatoprotective effects of *Rubus aleaefolius* Poir. And identification of its active constituents. *Journal of Ethnopharmacology*, Vol 129, No.2, pp. 267– 272, ISSN 0378-8741

Hu, H. L. & Chen, R. D. (1992). Changes in free radicals, trace elements, by d-galactosamine. *Biological Trace Element Research*, Vol 34, No.1 ,pp. 19– 25, ISSN 0163-4984

Huang, B.; Ban, X.; He, J.; Tong, H.; Zhang, J.; Tian, J. & Wang, Y. (2010a). Hepatoprotective and antioxidant activity of ethanolicextracts of edible lotus (*Nelumbo nucifera* Gaertn.) leaves. *Food Chemistry*, Vol 120, No.3, pp. 873–878, ISSN 0308-8146

Huang, B.; Ban, X.; He, J.; Zeng, H.; Zhang, P. & Wang, Y. (2010b). Hepatoprotective and antioxidant effects of the methanolic extract from *Halenia elliptica. Journal of Ethnopharmacology*, Vol 131, No.2, pp. 276– 281, ISSN 0378-8741

Ip, S.-P.; Woo, K.-Y.; Lau, O.-W. & Che1, C.-T. (2004). Hepatoprotective Effect of *Sabina przewalskii* against Menadione-induced Toxicity. *Phytotherapy Research,* Vol 18, No.4, pp. 329–331, ISSN 0951-418X

Iyer, R.S.; Voehler, M.W. & Harris, T.M. (1994). Adenine adduct of Aflatoxin B1 epoxide. *J. Am. Chem. Soc.,* Vol 116, No.20, pp. 8863–8869, ISSN 0002-7863

Jain, A.; Soni, M.; Deb, L.; Jain, A.; Rout, S. P.; Gupta, V. B. & Krishna, K. L. (2008). Antioxidant and hepatoprotective activity of ethanolic and aqueous extracts of *Momordica dioica* Roxb. Leaves. *Journal of Ethnopharmacology*, Vol 115, No.1, pp. 61–66, ISSN 0378-8741

Jaishree, V. & Badami, S. (2010). Antioxidant and hepatoprotective effect of swertiamarin from Enicostemma axillare against d-galactosamine induced acute liver damage in rats. *Journal of Ethnopharmacology*, Vol 130, No.1, pp. 103– 106, ISSN 0378-8741

Jamshidzadeh, A.; Fereidooni, F.; Salehi, Z. & Niknahad, H. (2005). Hepatoprotective activity of *Gundelia tourenfortii*. *Journal of Ethnopharmacology*, Vol 101, No.1-3, pp. 233-237, ISSN 0378-8741

Karthikeyan, M. & Deepa, K. (2010). Hepatoprotective effect of *Premna corymbosa* (Burn. F.) Rottl. & Willd. Leaves extract on $CCl_4$ induced hepatic damage in Wistar albino rats. *Asian Pacific Journal of Tropical Medicine*, Vol 3, No.1, pp. 17- 20, ISSN 16879686

Keppler, D. O.; Rudigier, J. F.; Bischoff, E. & Decker, K. (1970). The trapping of uridine phosphates by d-galactosamine, d-glucosamine, and 2-deoxy-d-galactose.Astudy on the mechanism of galactosamine hepatitis. *European Journal of Biochemistry*, Vol 17, No.2, pp. 246– 253, ISSN 0014-2956

Kim, W. R.; Brown, R. S.; Terrault, N. A. & El-Serag, H. (2002). Burden of liver disease in the United States: Summary of work-Shop. *Hepatology*, Vol 36, No.1, pp. 227-242, ISSN 0270-9139

Khatri, A.; Garg, A. & Agrawal, S. A. (2009). Evaluation of hepatoprotective activity of aerial parts of *Tephrosia purpurea* L. and stem bark of *Tecomella undulate. Journal of Ethnopharmacology*, Vol 122, No.1, pp. 1–5, ISSN 0378-8741

Kmieć, Z.; Ryszard Smoleński, R. T.; Zysh, M. & Myśliwski, A. (2000). The effects of galactosamine on UTP levels in the livers of young, adult and old rats. *Acta Biochimica Polonica*, Vol 47, No.2, pp. 349- 353, ISSN 0001-527X

Kumar, S. S.; Kumar, B. R. & Mohan G. K. (2009). Hepatoprotective effect of *Trichosanthes cucumerina* Var *cucumerina* L. on carbon tetrachloride induced liver damage in rats. *Journal of Ethnopharmacology,* Vol 123, No.2, pp. 347–350, ISSN 0378-8741

Leaver, M. J. & George, S. G. (1998). A piscine glutathione S-transferase which efficiently conjugates the end-products of lipid peroxidation. *Marine Environmental Research,* Vol 46, No.1-5, pp. 71–74, ISSN 0141-1136

Madubunyi, I. I. (2010). Hepatoprotective activity of *Uvaria chamae* root bark methanol extract against acetaminophen-induced liver lesions in rats. *Comparative Clinical Pathology*, In Press, ISSN 1618-5641

Maheswari, M. U. & Rao, P. G. M. (2005). Anti hepatotoxic effect of grape seed oil. *Indian Journal of Pharmacology*, Vol 37, No.3, pp. 179- 182, ISSN 0253-7613

Marina, N. (2006). Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. *Journal of Hepatology*, Vol 44, No.1, pp. S132–S139, ISSN 0168-8278

McConnachie, L. A.; Mohar, I.; Hudson, F. N.; Ware, C. B.; Ladiges, W. C.; Fernandez, C.; Chatterton-Kirchmeier, S.; White, C. C.; Pierce, R. H. & Kavanagh, T. J. (2007). Glutamate cysteine ligase modifier subunit deficiency and gender as determinants of acetaminophen-induced hepatotoxicity in mice. *Toxicological Scinces,* Vol 99, No.2, pp. 628–636, ISSN 1096-6080

McCuskey, R. S. (2006). Anatomy of the liver. In: *Zakim and Boyer's Hepatology*, T. D. Boyer; T. L. Wright; M. Manns, (Eds.), 37, 5th ed., Saunders–Elsevier, Philadephia.

Mitchell, J. R.; Jollow, D. J.; Potter, W. Z.; Gillete, J. R. & Brrodle, B.N. (1973). Acetaminophen induced hepatic necrosis. I. Role of drug metabolism. *Journal of Pharmacology and Experimental Therapeutics*, Vol 187, No.1, pp. 185–194, ISSN 0022-3565

Mohamed, M. A.; Marzouk, M. S. A.; Moharram, F. A.; El-Sayed, M. M. & Baiuomy A. R. (2005). Phytochemical constituents and hepatoprotective activity of *Viburnum tinus*. *Phytochemistry*, Vol 66, No.23, pp. 2780–2786, ISSN 1819-3471

Moncada, S. & Erusalimsky, J. D. (2002). Does nitric oxide modulate mitochrondrial energy generation and apoptosis? *Nature Reviews Molecular Cell Biology*, Vol 3, pp. 214–220, ISSN 1471-0072

Morazzoni, P. & Bombardelli, E. (1995). *Silybum marianum*. *Fitoterapia,* Vol 66, No.1, pp. 3–42, ISSN 0367-326X

Morikawa, T.; Pan, Y.; Ninomiya, K.; Imura, K.; Matsuda, H.; Yoshikawa, M.; Yuan, D. & Muraoka, O. (2010). Acylated phenylethanoid oligoglycosides with hepatoprotective activity from the desert plant *Cistanche tubulosa*. *Bioorganic & Medicinal Chemistry*, Vol 18, No.5, pp. 1882–1890, ISSN 0960-894X

Naaz, F.; Javed, S. & Abdin, M. Z. (2007). Hepatoprotective effect of ethanolic extract of *Phyllanthus amarus* Schum. et Thonn. on aflatoxin B1-induced liver damage in mice. *Journal of Ethnopharmacology*, Vol 113, No.3, pp. 503–509, ISSN 0378-8741

Navarro, V. J. & Senior, J. R. (2006). Drug-related hepatotoxicity. *New England Journal of Medicine*, Vol 35, No.4, pp. 731–739, ISSN 0028-4793

Nishigaki, I.; Kuttan, R.; Oku, H.; Ashoori, F.; Abe, H. & Yagi, K. (1992). Suppressive effect of curcumin on lipid peroxidation induced in rats by $CCl_4$ or $^{60}Co$ irradiation. *Journal of Clinical Biochemistry and Nutrition,* Vol 13, pp. 23- 30, ISSN 0912-0009

Noh J.-R.; Kim, Y.-H.; Gang, G.-T.; Hwang, J. H.; Lee, H.-S.; Ly, S,-Y.; Oh, W.-K.; Song, K.-S.& Lee, C.-H. (2011). Hepatoprotective effects of chestnut (*Castanea crenata*) inner shell extract against chronic ethanol-induced oxidative stress in C57BL/6 mice. *Food and Chemical Toxicology*, In Press, ISSN 0278-6915

Nussler, A.; DiSilvio, M.; Billiar, T. R.; Hoffman, R. A.; Geller, D. A.; Selby, R.; Madariaga, J. & Simmons R. L. (1992). Stimulation of the nitric oxide synthase pathway in human hepatocytes by cytokines and endotoxin. *Journal of Experimental Medicine*, Vol 176, pp. 261-264, ISSN 0022-1007

Nyblom, H.; Berggren, U.; Balldin, J. & Olsson, R. (2004). High AST/ALT ratio may indicate advanced alcoholic liver disease rather than heavy drinking. *Alcohol & Alcoholism,* Vol 39, No.4, pp. 336- 339, ISSN 0735-0414

Obioha, U. E.; Suru, S. M.; Ola-Mudathir, K. F. & Faremi, T. Y. (2009). Hepatoprotective potentials of Onion and Garlic extracts on Cadmium-Induced oxidative damage in rats. *Biological Trace Element Research*, Vol 129, No.1-3, pp. 143–156, ISSN 0163-4984

Olinescu, R.; Alexandrescu, R.; Hulea, S. A. & Kummerow, F. A. (1994). Tissue lipid peroxidation may be triggered by increased formation of bilirubin *in vivo*. *Research Communications in Chemical Pathology & Pharmacology*, Vol 84, No.1, pp. 27-34, ISSN 0034-5164

Owvens, D. & Evans, J. (1975). Population studies on Gilbert's syndrome. *Journal of Chemical Genetics*, Vol 12, pp. 152- 156, ISSN 0104-6632

Özbek, H.; Çitoğlu, G. S.; Dülger, H.; Uğraş, S. & Sever, B. (2004). Hepatoprotective and anti-inflammatory activities of *Ballota glandulosissima. Journal of Ethnopharmacology,* Vol 95, No.2-3, pp. 143–149, ISSN 0378-8741

Palmer, R. M. J.; Ashton, D. S.; & Moncada, S. (1988). Vascular endothelial cells synthesis nitric oxide from L-arginine. *Nature,* Vol 333, No.6174, pp. 664-666, ISSN 0028-0836

Pastore, A.; Piemonte, F.; Locatelli, M.; Russo, A. L.; Gaeta, L. M.; Tozzi, G.& Federici, G. (2003). Determination of blood total, reduced, and oxidized glutathione in pediatric subjects. *Clinical Chemistry,* Vol 47, No.8, pp. 1467–1469, ISSN 0009-9147

Perry, G.; Raina, A. K.; Nunomura, A.; Wataya T.; Sayre, L. M. & Smith M. A. (2000). How important is oxidative damage? Lessons from Alzheimer's disease. *Free Radical Biology and Medicine,* Vol 28, No.5, pp. 831-834, ISSN 0891-5849

Pompella, A.; Visvikis, A.; Paolicchi, A.; de Tata, V. & Casini, A. F. (2003). The changing faces of glutathione, a cellular protagonist. *Biochemical Pharmacology,* Vol 66, No.8, pp. 1499–503, ISSN 0006-2952

Porchezhian, E. & Ansari, S. H. (2005). Hepatoprotective activity of *Abutilon indicum* on experimental liver damage in rats. *Phytomedicine,* Vol 12, No.1-2, pp. 62–64, ISSN 0944-7113

Pramyothin, P.; Ngamtin, C.; Poungshompoo, S. & Chaichantipyuth, C. (2007). Hepatoprotective activity of *Phyllanthus amarus* Schum. et. Thonn. extract in ethanol treated rats: *In vitro* and *in vivo* studies. *Journal of Ethnopharmacology*, Vol 114, No.2, pp. 169–173, ISSN 0378-8741

Prophet, E. P.; Mills, B.; Arrington, J. B. & Sobin, L. H. (1994). *Laboratory Methods in Histology*. 1st Ed, American Registry of Pathology, Washington, D.C.

Purohit, V.; Gao, B. & Song, B.-J. (2009). Molecular Mechanisms of Alcoholic Fatty Liver. *Alcohol.: Clin. Exp. Res.*, Vol 33, No.2, pp. 191–205, ISSN 1530-0277

Quintero, A.; Pedraza, C. A.; Siendones, E.; Kamal, E. A. M.; Colell, A.; García -Ruiz, C.; Montero, J. L.; Dela, M. M.; Fernández-Checa, J. C.; Miño, G.; Muntane´ , J.; Kamal, E. A. M. & Colell, A. (2002). PGE1 protection against apoptosis induced by D-galactosamine is not related to the modulation of intracellular free radical production in primary culture of rat hepatocytes. *Free Radical Research*, Vol 36, No.3, pp. 345–355, ISSN 1071-5762

Qureshi, N. N.; Kuchekar, B. S.; Logade, N. A. & Haleem, M. A. (2009). Antioxidant and hepatoprotective activity of *Cordia macleodii* leaves. *Saudi Pharmaceutical Journal*, Vol 17, No.4, pp. 299– 302, ISSN 1319-0164

Rafatullah, S.; Al-Sheikh, A.; Alqasoumi, S.; Al-Yahya, M.; El-Tahir, K. & Galal, A. (2008). Protective effect of fresh radish juice (*Raphanus sativus* L.) against carbon

tetrachloride-induced hepatotoxicity. *International Journal of Pharmacology*, Vol 4, No.2, pp. 130- 134. ISSN 1811-7775.

Rafatullah, S.; Mossa, J. S.; Ageel, A. M.; Al-Yahya, M. A. & Tariq, M. (1991). Hepatoprotective and safety evaluation studies on Sarsaparilla. *International Journal of Pharmacognosy (Now Pharmaceutical Biology)*, Vol 29, No.4, pp. 296- 301, ISSN 1388-0209

Ram, V. J. (2001). Herbal preparations as a source of hepatoprotective agents. *Drug News and Perspective,* Vol 14, No.6, pp. 353-363. ISSN 0214-0934

Ranawat, L.; Bhatt, J. & Patel J. (2010). Hepatoprotective activity of ethanolic extracts of bark of *Zanthoxylum armatum* DC in CCl4 induced hepatic damage in rats. *Journal of Ethnopharmacology*, Vol 127, No.3, pp. 777–780, ISSN 0378-8741

Rao, P. G. M.; Rao, S. G. & Kumar, V. (1993). Effects of hepatogard against carbon tetrachloride induced liver damage in rats. *Fitoterapia*, Vol 64, No.2, pp. 108-113, ISSN 0367-326X

Rathi, M. A.; Thirumoorthi, L.; Sunitha, M.; Meenakshi, P.; Gurukumar, D. & Gopalakrishnan, V. K. (2010). Hepatoprotective activity of *Spermacoce hispida* Linn. extract against nitrobenzene induced hepatotoxicity in rats. (2010). *Journal of Herbal Medicine and Toxicology*, Vol 4, No.2, pp. 201-205, ISSN 0973-4643.

Rathi, A., Srivastava, A. K.; Shirwaikar, A.; Rawat, A. K. S. & Mehrotra S. (2008). Hepatoprotective potential of *Fumaria indica* Pugsley whole plant extracts, fractions and an isolated alkaloid protopine. *Phytomedicine*, Vol 15, pp. 470– 477, ISSN 0944-7113

RCSB Protein Data Bank. Catalase. *Molecule of the Month*. (2004-09-01). Retrieved on 2007-02-11, http://www.pdb.org/pdb/101/motm.do?momID=57

Recknagel, R. O. & Glende, E. A. Jr. (1973). Carbon tetrachloride hepatotoxicity: an example of lethal cleavage. CRC (*Critical Reviews in Toxicology*). Vol. 2, No.3, pp. 263-297, ISSN 1040-8444

Recknagel, R. O.; Glonde, E. A.; Dolak, J. A. & Walter, R. L. (1989). Mechanism of carbon tetrachloride toxicity. *Pharmacology and Therapeutics*, Vol 43, No.1, pp. 139–154, ISSN 0163-7258

Remirez, D.; Commandeur, J. N. M.; Ed Groot, E. & Vermeulen, N. P. E. (1995). Mechanism of protection of *Lobenzarti* against paracetamol-induced toxicity in rat hepatocytes. *European Journal of Pharmacology: Environmental Toxicology and Pharmacology*, Vol 293, No.4, pp. 301- 308, ISSN 0926-6917

Rivett, A. J. & Levine, R. L. (1990): Metal-catalyzed oxidation of Escherichia coli glutamine synthetase: correlation of structural and functional changes. *Archives of Biochemistry and Biophysics*. Vol 278, No.1, pp. 26- 34, ISSN 0003-9861

Sabir, S. M.& Rocha, J. B. T. (2008). Antioxidant and hepatoprotective activity of aqueous extract of *Solanum fastigiatum* (false "Jurubeba") against paracetamol-induced liver damage in mice. *Journal of Ethnopharmacology*, Vol 120, No.2, pp. 226– 232, ISSN 0378-8741

Sadasivan, S.; Latha, P. G.; Sasikumar, J. M.; Rajashekaran, S.; Shyamal, S. & Shine, V. J. (2006). Hepatoprotective studies on *Hedyotis corymbosa* (L.) Lam. *Journal of Ethnopharmacology*, Vol 106, No.2, pp. 245– 249, ISSN 0378-8741

Saller, R.; Melzer, J.; Reichling, J.; Brignoli, R. & Meier, R. (2007). An updated systematic review of the pharmacology of silymarin. *Forschende Komplementmedizin (Research in Complementary Medicine)*, Vol 14, No.2, pp. 70- 80, ISSN 1661-4119

Sallie, R.; Tredger, J. M. & William, R. (1991). *Drugs and the liver. Part I. Testing liver function. Biopharmaceutics & Drug Disposition,* Vol 12, No.4, pp. 251- 259, *ISSN* 0142-2782

Salmi, H. A. & Sarna S. (1982). Effect of silymarin on chemical, functional, and morphological alterations of the liver. A double-blind controlled study. *Scandinavian Journal of Gastroenterology*, Vol17, No.4, pp. 517– 521, ISSN 0036-5521

Sathaye, S., Bagul, Y.; Gupta, S.; Kaur, H. & Roopali Redkar, R. (2010). Hepatoprotective effects of aqueous leaf extract and crude isolates of *Murraya koenigii* against *in vitro* ethanol-induced hepatotoxicity model. *Experimental and Toxicologic Pathology*, In Press, ISSN 0940-2993

Scott, M. D.; Lubin, B. H.; Zuo, L. & Kuypers, F. A. (1991). Erythro-cyte defense against hydrogen peroxide: preeminent importance of catalase. *Journal of Laboratory and Clinical Medicine*, Vol 118, No.1, 7– 16, ISSN 0022-2143

Sen, T.; Basu, A.; Ray, R. N. & Nag Shaudhuri, A. K. (1993). Hepatoprotective effects of *Pluchea indica* (Lees) extract in experimental acute liver damage in rodents. *Phytotherapy Research*, Vol 7, No.5, pp. 352-355, ISSN 0951-418X

Setty, S. R.; Quereshi, A. A.; Swamy, A. H. M. V.; Patil, T.; Prakash, T.; Prabhu, K. & Gouda, A. V. (2007). Hepatoprotective activity of *Calotropis procera* flowers against paracetamol-induced hepatic injury in rats. *Fitoterapia*, Vol 78, pp. 451– 454, ISSN 0367-326X

Shankar, N. L. G.; Manavalan, R.; Venkappayya, D. & Raj, C. D. (2008). Hepatoprotective and antioxidant effects of *Commiphora berryi* (Arn) Engl bark extract against CCl4-induced oxidative damage in rats. *Food and Chemical Toxicology*, Vol 46, No.9, pp. 3182– 3185, ISSN 0278-6915

Shanmugasundaram, P. & Venkataraman, S. (2006). Hepatoprotective and anti oxidant effects of *Hygrophila Auriculta* (K. Schum) Heine Acanthaceae root extract. *Journal of Ethnopharmacology*, Vol 104, No.1-2, pp. 124- 128, ISSN 0378-8741

Sharma, N. & Shukla, S. (2010). Hepatoprotective potential of aqueous extract of *Butea monosperma* against CCl4 induced damageinrats. *Experimental and Toxicologic Pathology*, In Press, ISSN 0940-2993

Shi, J.; Aisaki, K.; Ikawa, Y. & Wake, K., (1998). Evidence of hepatocyte apoptosis in rat liver after administration of carbon tetrachloride. *American Journal of Pathology*, Vol 153, No.2, 515– 525, ISSN 0002-9440

Shi, Y.; Sun J.; He, H.; Guo, H. & Zhang, S. (2008). Hepatoprotective effects of *Ganoderma lucidum* peptides against d-galactosamine-induced liver injury in mice. *Journal of Ethnopharmacology*, Vol 117, No.3, pp. 415– 419, ISSN 0378-8741

Shilova, I. V.; Zhavoronok, T. V.; Souslov, N. I.; Novozheeva, T. P.; Mustafin, R. N. & Losseva, A. M. (2008). Hepatoprotective Properties of Fractions from Meadowsweet Extract during Experimental Toxic Hepatitis. *Bulletin of Experimental Biology and Medicine, Pharmacology and Toxicology*, Vol. 146, No.1, pp. 49- 51, ISSN 1535-3702

Shiratori, Y.; Kawase, T.; Shiina, S.; Okano, K.; Sugimoto, T.; Teraoka, H.; Matano, S.; Matsumoto, K. & Kamii, K. (1988). Modulation of hepatotoxicity by macrophages in the liver. *Hepatology*, Vol 8, No.4, pp. 815– 821, ISSN 0270-9139

Shyamal, S.; Latha, P. G.; Shine, V. J.; Suja, S. R.; Rajasekharan S. & Devi, T. G. (2006). Hepatoprotective effects of *Pittosporum neelgherrense* Wight&Arn., a popular Indian ethnomedicine. *Journal of Ethnopharmacology,* Vol 107, No.1, pp. 151– 155, ISSN 0378-8741

Singh, B; Saxena, A. K.; Chandan, B. K.; Agrawal, S. G. & Anand, K. K. (2001). In vivo hepatoprotective activity of active fraction from ethanolic extract of *Eclipta alba* leaves. *Indian Journal of Physiology and Pharmacology*, Vol 45, No.4, pp. 435– 441, ISSN 0019-5499

Slater, T. F. (1965). *Biochemical mechanism of liver injury*. London: Academic Press.

Snyder, R. & Andrews, L. S. (1996). Toxic effects of solvents and vapors. In: *Toxicology: the Basic Science of Poisons,* C. D. Klassen, (Ed.), 737–772, McGraw-Hill, New York.

Somasundaram, A.; Karthikeyan, R.; Velmurugan, V.; Dhandapani, B. & Raja, M. (2010). Evaluation of hepatoprotective activity of *Kyllinga nemoralis* (Hutch & Dalz) rhizomes. *Journal of Ethnopharmacology*, Vol 127, No.2, pp. 555– 557, ISSN 0378-8741

Souza, M. F.; Rao, V. S. N. & Silveira, E. R. (1997). Inhibition of lipid peroxidation by ternatin, a tetramethoxyflavone from *Egletes viscosa* L. *Phytomedicine*, Vol 4, pp. 25–9, ISSN 0944-7113

Sreedevi, C. D.; Latha, P. G.; Ancy, P.; Suja, S. R.; Shyamal, S.; Shine, V. J.; Sini, S.; Anuja, G. I. & Rajasekharan, S. (2009). Hepatoprotective studies on *Sida acuta* Burm. f. *Journal of Ethnopharmacology*, Vol 124, No.2, pp. 171– 175, ISSN 0378-8741

Subramoniam, A. & Pushpangadan, P. (1999). Development of phytomedicine for liver diseases. *Indian Journal of Pharmacology*, Vol 31, No.3, pp. 166–175, ISSN 0253-7613

Suja, S. R.; Latha, P. G.; Pushpangadan, P. & Rajasekharan, S. (2004). Evaluation of hepatoprotective effects of *Helminthostachys zeylanica* (L.) Hook against carbon tetrachloride-induced liver damage in Wistar rats. *Journal of Ethnopharmacology*, Vol 92, No.1, pp. 61– 66, ISSN 0378-8741

Suzuki, I.; Tanaka, H.; Yajima, H.; Fukuda, H.; Sezaki, H.; Koga, K.; Hirobe, M. & Nakajima, T. (1990). *Pharmaceutical Research and Development*, Vol 19, 227, Hirokawa Publishing, Tokyo.

Tandogan, B. & Ulusu, N. N. (2006). Kinetic Mechanism and Molecular Properties of Glutathione Reductas, *FABAD Journal of Pharmaceutical Sciences*, Vol 31, pp. 230-237. ISSN 1300-4182.

Tandon, V. R.; Khajuria, V.; Kapoor, B.; Kour, D. & Gupta, S. (2008). Hepatoprotective activity of *Vitex negundo* leaf extract against anti-tubercular drugs induced hepatotoxicity. *Fitoterapia*, Vol 79, pp. 533– 538, ISSN 0367-326X

Tiegs, G., Wolter, M. & Wendel, A. (1989). Tumor necrosis factor is a terminal mediator in galactosamine/endotoxin-induced hepatitis in mice. *Biochemical Pharmacology*, Vol 38, No.4, pp. 627- 631, ISSN 0006-2952

Udomsinprasert, R.; Pongjaroenkit, S.; Wongsantichon, J.; Oakley, A. J.; Prapanthadara, L. A.; Wilce, M. C. & Ketterman, A. J. (2005). Identification, characterization and structure of a new Delta class glutathione transferase isoenzyme. *Biochemical Journal,* Vol 388, No.3, pp. 763 – 771, ISSN 0264-6021

Vaca, C. E.; Wilhelm, J. & Harms-Rihsdahl, M. (1988). Interaction of lipid peroxidation product with DNA. A review. *Mutation Research-Reviews in Genetic Toxicology*, Vol 195, No.2, pp. 137– 149, ISSN 0165-1110

Valarmathi, R.; Rajendran, A.; Gopal, V.; Senthamarai, R.; Akilandeswari, S. & Srileka, B. (2010). Protective Effcet of the whole plant of *Mollugo pentaphylla* Linn. against Carbon Tetrachloride induced Hepatotoxicity in Rats. *International Journal of PharmTech Research*, Vol 2, No.3, pp. 1658-1661, ISSN 0974-4304

Venkatesh, P.; Dinakar, A. & Senthilkumar, N. (2011). Hepatoptotective activity of an ethanolic extract of stems of *Anisochilus carnosus* against carbon tetrachloride induced hepatotoxicity in rats. *International Journal of Pharmacy and Pharmaceutical Sciences*, Vol 3, No.1, pp. 243- 245, ISSN- 0975-1491

Vogel, G. (1977). Natural substances with effects on the liver, In: *New natural products and plant drugs with pharmacological, biological or therapeutic activity*. H. Wagner & P. Wolff (eds), pp 249–265, Springer-Verlag, Berlag, Heidelberg, New York.

Wagner, H.; Seligmann, O.; Horhammer, L. & Munster, R. (1968). The chemistry of silymarin (silybin), the active principle of the fruits of *Silybum marianum* (L.) Gaertn. [*Carduus marianus* (L.)]. *Arzneimittelforschung*, Vol 18, No.6, pp. 688– 696, ISSN 0004-4172

Wang, M. Y.; Liu, Q.; Che, Q. M. & Lin, Z. B. (2000). Effects of triterpenoids from *Ganoderma lucidum* (Leyss. Ex fr.) karst on three different experimental liver injury models in mice. *Acta Pharmaceutica Sinica*, Vol 35, No.5, pp. 326– 329, ISSN 0513-4870

Wang, N.; Li, P.; Wang, Y.; Peng, W.; Wu, Z.; Tan, S.; Liang, S.; Shen, X. & Su, W. (2008). Hepatoprotective effect of *Hypericum japonicum* extract and its fractions. *Journal of Ethnopharmacology*, Vol 116, No.1, pp. 1– 6, ISSN 0378-8741

Ward, F. M. & Daly, M. J. (1999). Hepatic Disease. In: *Clinical Pharmacy and Therapeutics*, R. Walker & C.Edwards (Eds.), 195- 212, Churchill Livingstone, New York.

Weber, L.W.; Boll, M. & Stampfl, A. (2003). Hepatotoxicity and mechanism of action of haloalkanes: carbon tetrachloride as a toxicological model. *Critical Reviews in Toxicology*, Vol 33, No.2, pp. 105– 136, ISSN 1040-8444

Wills, P. J. & Asha, V. V. (2006). Protective effect of *Lygodium.exuosum* (L.) Sw. (Lygodiaceae) against d-galactosamine induced liver injury in rats. *Journal of Ethnopharmacology*, Vol 108, No.1, pp. 116–123, ISSN 0378-8741

Witte, I.; Berlin, J.; Wray, V.; Schubert, W.; Kohl, W.; Hofle, G. & Hammer, J. (1983). Mono and diterpins from cell culture or *Thuja Occidenalis*. *Planta Medica,* Vol 49, pp. 216-221, ISSN 00320943

Wu, Y.; Yang, L.; Wang, F.; Wu, X.; Zhou, C.; Shi, S.; Mo, J. & Zhao, Y. (2007). Hepatoprotective and antioxidative effects of total phenolics from *Laggera pterodonta* on chemical-induced injury in primary cultured neonatal rat hepatocytes. *Food and Chemical Toxicology*, Vol 45, No.8, pp. 1349– 1355, ISSN 0278-6915

Ye, X.; Feng, Y.; Tong, Y.; Ng, K.-M.; Tsao, S.; Lau, G. K. K.; Sze, C.; Zhang, Y.; Tang, J.; Shen, J. & Kobayashi, S. (2009). Hepatoprotective effects of *Coptidis rhizoma* aqueous extract on carbon tetrachloride-induced acute liver hepatotoxicity in rats. *Journal of Ethnopharmacology,* Vol 124, No.1, pp. 130– 136, ISSN 0378-8741

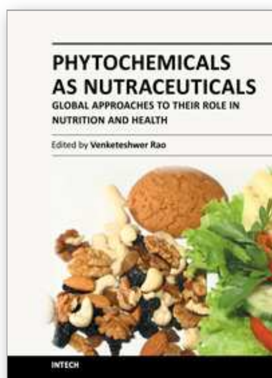
Yen, F.-L.; Wu, T.-H.; Lin, L.-T. & Lin, C.-C. (2007). Hepatoprotective and antioxidant effects of *Cuscuta chinensis* against acetaminophen-induced hepatotoxicity in rats. *Journal of Ethnopharmacology*, Vol 111, No.1, pp. 123–128, ISSN 0378-8741

Yuan, H.-D., Jin, G.-Z. & Piao, G.-C. (2010). Hepatoprotective effects of an active part from *Artemisia sacrorum* Ledeb. against acetaminophen-induced toxicity in mice. *Journal of Ethnopharmacology,* Vol 127, No.2, pp. 528– 533, ISSN 0378-8741

Zafar, R. & Ali, S. M. (1998). Anti-hepatotoxic effects of root and root callus extracts of *Cichorium intybus* L. *Journal of Ethnopharmacology*, Vol 63, No.3, pp. 227–231, ISSN 0378-8741

Zhou, D.; Ruan, J.; Cai, Y.; Xiong, Z.; Fu, W. & Wei, A. (2010). Antioxidant and hepatoprotective activity of ethanol extract of *Arachniodes exilis* (Hance) Ching. *Journal of Ethnopharmacology,* Vol 129, No.2, pp. 232– 237, ISSN 0378-8741

Zimmerman, H. J. & Seeff, L. B. (1970). Enzymes in hepatic disease. In: *Diagnostic Enzymology*. E. I. Goodly (Ed.), 1, Lea and Febiger, Philadelphia, USA.




**Phytochemicals as Nutraceuticals - Global Approaches to Their Role in Nutrition and Health**
Edited by Dr Venketeshwer Rao

ISBN 978-953-51-0203-8
Hard cover, 278 pages
**Publisher** InTech
**Published online** 23, March, 2012
**Published in print edition** March, 2012

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.

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Saleh I. Alqasoumi and Maged S. Abdel-Kader (2012). Screening of some Traditionally Used Plants for Their Hepatoprotective Effect, Phytochemicals as Nutraceuticals - Global Approaches to Their Role in Nutrition and Health, Dr Venketeshwer Rao (Ed.), ISBN: 978-953-51-0203-8, InTech, Available from: http://www.intechopen.com/books/phytochemicals-as-nutraceuticals-global-approaches-to-their-role-in-nutrition-and-health/review-screening-of-some-traditionally-used-plants-for-their-hepatoprotective-effect

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