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BIOACTIVE PHYTOCONSTITUENTS WITH HEPATOPROTECTIVE POTENTIAL: A REVIEW

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ABSTRACT

The liver is a requisite organ in the body, maintaining various physiological functions. Liver damage or toxicity is due to consuming certain chemicals, dietary supplements, drugs, and alcohol at high doses in day-to-day life. Several phytoconstituents acts as hepatoprotective agents. Research advances in analytical techniques and knowledge of active components have allowed research scientists to study the relationship between the phytoconstituents and their activity on the human liver. The review article aims to compile data on promising active constituents that act as lead molecules for future natural products-based drug discovery. The online database, including Web of Science, PubMed, Scopus, and Science Direct, was explored for papers and studied the hepatoprotective activity. Some phytoconstituents act against the chemicals such as CCl_4, paracetamol, alcohol, oxidative stress-induced hepatotoxicity, etc.

Keywords : Hepatoprotective, phytoconstituents, *in-vitro* and *in-vivo* studies.

INTRODUCTION

The liver occupies a significant portion of our body that involves several vital functions, such as metabolism, secretion, and storage. The liver detoxifies many exogenous and endogenous compounds. The liver acts as a reservoir for proteins, glycogen, various vitamins, and metals. It also features a role in regulating blood volume by transferring the blood from the portal to the circulation and its reticuloendothelial system and participating in the immune mechanism. Most drugs are considered foreign substances (xenobiotics) by the body, which involves metabolism and elimination (llyas *et al*., **2016**).

It involves chemical transformations, mainly

a) To reduce fat solubility and

b) To change biological activity.

The liver's vital role in the clearance and transformation of chemicals also makes it susceptible to drug-induced liver injury. The disruption of liver processes can lead to hepatotoxicity, causing liver cancer, cirrhosis, and Hepatitis, respectively (Sumeet *et al*., **2019**). Liver damage leads to several other health issues of the affected person. Worldwide, approximately two million deaths (one million deaths are due to cirrhosis complications and one million are due to hepatitis and hepatocellular carcinoma) are reporting every year. About 75 million are diagnosed with alcohol use disorders and are at risk of alcohol-associated liver disease. Approximately 2 billion adults are obese, and over 400 million have diabetes; both consider as high-risk factors for hepatocellular carcinoma and fatty liver diseases. Hepatitis is an inflammation of the liver that can cause a range of health problems and be fatal (WHO, **2020**).

Biochemical markers

The liver's abnormality is monitor by some of the enzymes and the end products of the metabolic pathway, which are very sensitive and are considered biochemical markers. Liver function tests useful in the diagnosis and monitoring of disease or damage that occurred. The blood sample was collected, and detection tests for proteins and certain enzyme levels are measured (Poojari *et al*., 2010). Levels that are higher or lower than usual can indicate liver problems. Some standard liver function tests include:

Alkaline phosphatase (ALP) : Alkaline phosphatase is an enzyme that exists near the liver and bone and helps in breaking down proteins. Higher than normal ALP levels may indicate liver damage or disease, like a blocked common bile duct or certain bone diseases.

Alanine transaminase (ALT) : Alanine transaminase is also known as Glutamate pyruvate transaminase (GPT). It is an enzyme found in the hepatic system that helps in the conversion of proteins into energy. When the liver is damaged, the ALT level is high in the bloodstream.

Aspartate transaminase (AST) : Aspartate transaminase (AST) is also called Glutamate oxaloacetate transaminase (GOT). It is an enzyme that helps in amino acid metabolism. Like ALT, AST is generally present in blood at low levels. A rise in AST levels can detect liver damage.

Albumin and total protein : Albumin is one of the globular proteins made in the liver. The human body needs these

proteins to fight against certain infections and to perform other functions. A decrease in albumin and protein content indicates liver damage.

Bilirubin : Bilirubin may be a substance produced during the catabolic pathway after the breakdown of erythrocytes. Elevated levels of bilirubin leads to jaundice might indicate liver damage or disease.

Gammaglutamyltransferase (GGT) : Gamma-glutamyltransferase (GGT) is an enzyme found in several organs throughout the body, but the highest concentration level will be in the liver. Higher than normal levels indicates liver damage.

Lactate dehydrogenase (LDH) : Lactate dehydrogenase (LDH) is an enzyme required for the conversion of sugar molecules into energy. LDH is an enzyme found throughout the body, including the liver, heart, pancreas, kidneys, etc.; High levels of LDH indicate liver damage.

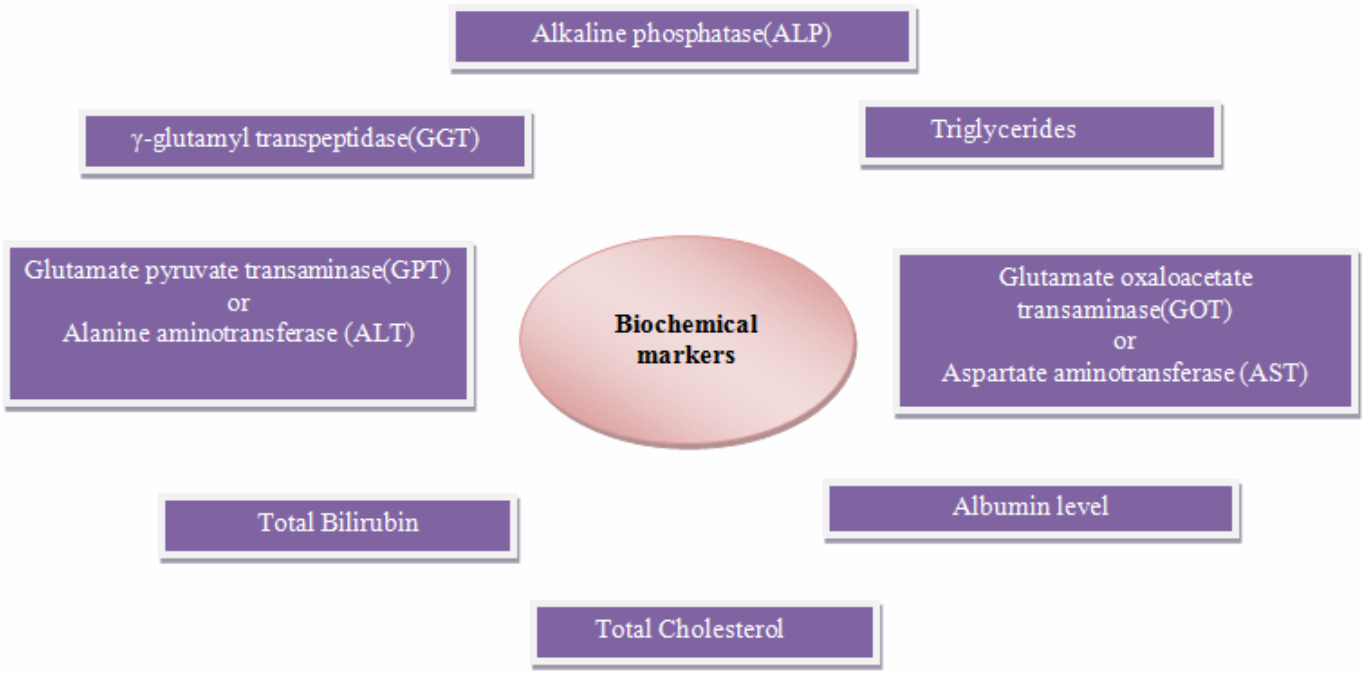

Fig 1: liver function tests

Natural products:

The compounds obtained from natural sources have good therapeutic activity and act as lead molecules in drug discovery. The advancement in technologies allows scientists to screen the new molecules. Overall, the natural products enhanced with 'bioactive' compounds covering a broader chemical space area than typical synthetic molecules. The complexity of structures can be advantageous for generating structural analogs to explore structure-activity relationships (SAR) and to optimize the compounds. Natural products remain an excellent scope for discovering scaffolds with high structural diversity and various bioactivities, which can act directly as a drug or acts as starting points for optimizing novel drugs. The scientific and technological advances in natural products-based drug discovery lead to significant contributions to human health (Atanasov *et al*., **2021**).

Chemical constituents with hepatoprotective activity:

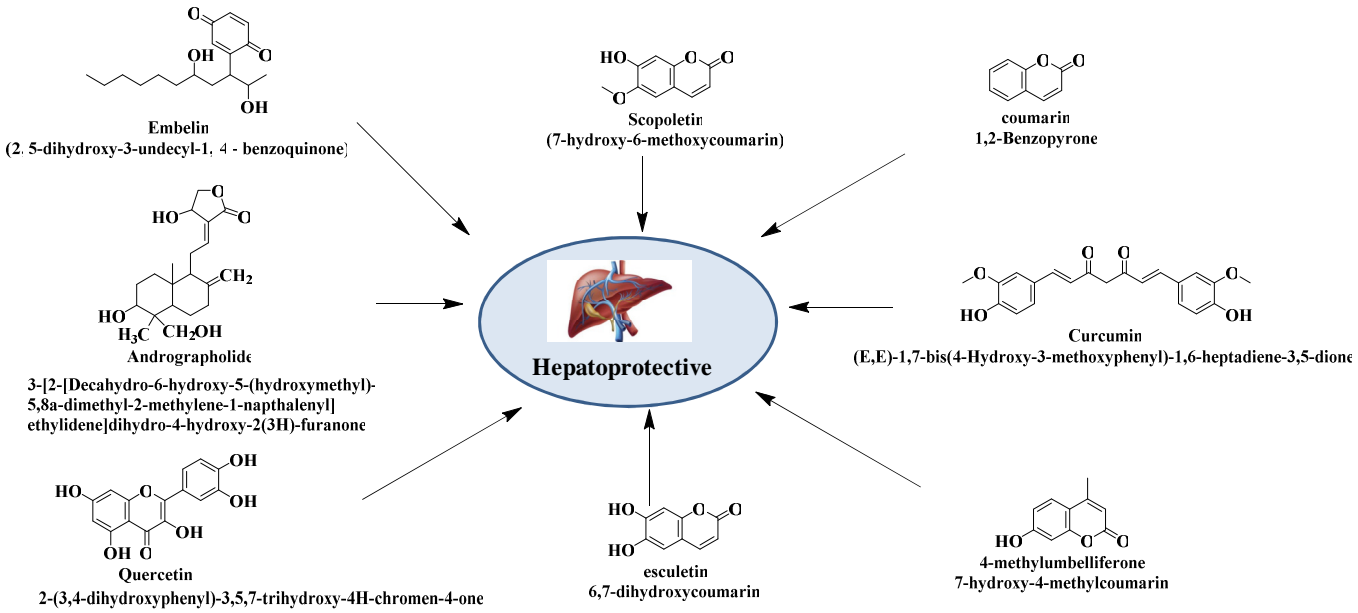

Fig 2: Hepatoprotective activity of active constituents

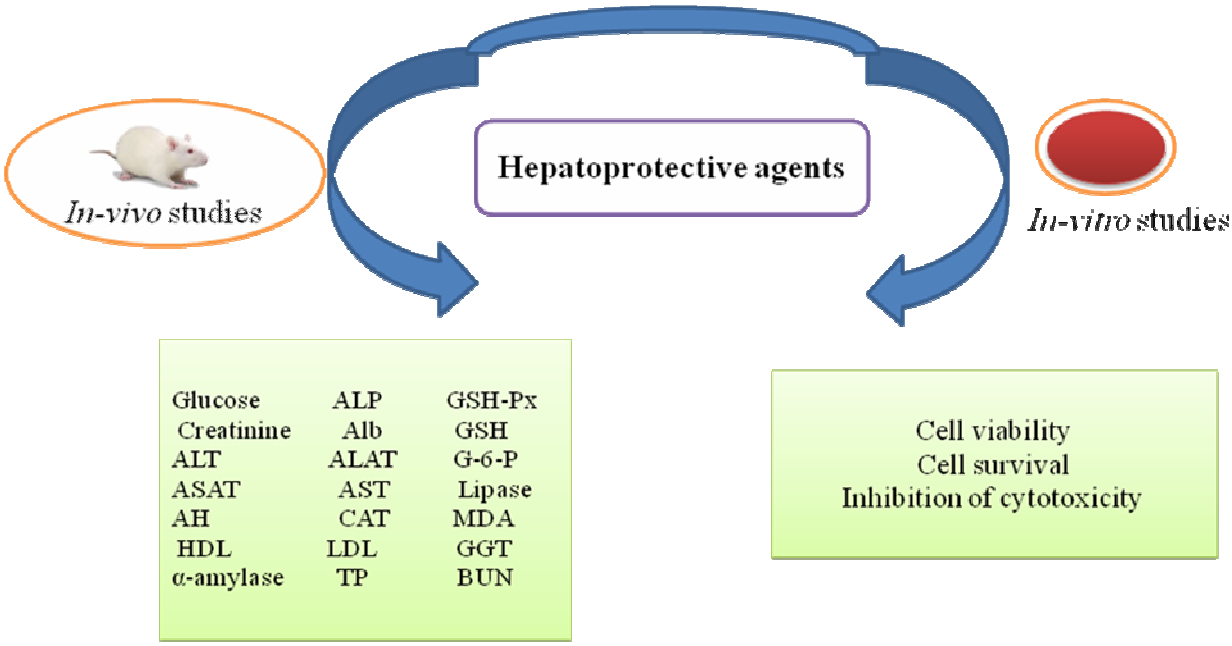

Fig 3: Studies conducted to determine the hepatoprotective agents (Pereira *et al*., 2016)

Effects of active constituents on the hepatic system:

Embelin:

Embelin is a (2,5-dihydroxy-3-undecyl-1,4-benzoquinone) naturally occurring para-benzoquinone. Embelin was investigated and reported for its hepatoprotective activity. Embelin acts against N-nitrosodiethylamine (NDEA) induced or carbon tetrachloride (CCl_4) induced liver damage. Embelin shows a protective effect on acute liver injury. Another study investigated by administering embelin via an intragastric gavage. 50ug/g mice body weight starting two days before thioacetamide (TAA) administration and continuing throughout the study. The liver functions, assessed by alkaline phosphatase activity/serum alanine aminotransferase. Lipid peroxidation and free radical scavenging activity of embelin against liver damage in rats studied. The study was conducted for 1-15 days by oral administration (25mg/kg). The observations proved that reduction of peroxidative damage in carbon tetrachloride (CCl_4) treated rats. Both liver and serum, along with effectively inducing the antioxidant potential (Gupta *et al*., 1977; Singh *et al*., 2009; Wang *et al*., 2019).

Scopoletin:

Scopoletin (7-hydroxy-6-methoxycoumarin) acts as a hepatoprotective agent. The research study conducted with altering concentration ranges from 1 µM to 50 µM on primary cultured rat hepatocytes. It significantly reduced the release of glutamic pyruvic transaminase and sorbitol dehydrogenase. The reported data revealed that at the concentration of 10 µM, scopoletin significantly preserved glutathione content by 50% and the activity of superoxide dismutase by 36% and also inhibited the production of malondialdehyde (Kang *et al*., **1998**).

Curcumin:

Curcumin ((E,E)-1,7-bis(4-Hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione).It is also known as the yellow

pigment of turmeric. It possesses anticarcinogenic, anti-inflammatory, hepatoprotective and antioxidant properties. The scientific reports demonstrate that curcumin has a high therapeutic ability for treating hepatic disorders (Garcia-Nino *et al*., 2014; Khana *et al*., 2019). Hepatoprotective effects of curcumin are mostly due to its antioxidant properties. Consumption of curcumin leads to a reduction in structural alterations of the hepatic system and total bilirubin. It decreases in ALT, AST, ALP, LDH, GGT activities and increases in serum proteins. It showed positive results in the management of cholestasis, hepatic fibrosis, and hepatic cancers (Nabavi *et al*., 2013).

The previously reported data shows the protective action of curcumin against experimental models of liver diseases. It has shown that treatment with dietary curcumin reduced fatty liver, necrosis, and inflammation. Curcumin is also known to inhibit oxidative stress and lipid peroxidation, activation of NF-kB, and the expression of IL-12, TNF-α, MCP-1, MIP-2, COX-2 and iNOS (Nanji *et al*., 2003). Swiss albino male mice used for the study, oral doses of Chloroquine phosphate (100mg/kg body wt., 200mg/kg body wt. and 300mg/kg body wt.) and chloroquine phosphate + curcumin (300mg/kg body wt+80mg/kg body wt.) administered for 45 days (Dattani *et al*., 2010; Hemeida *et al*., 2008).

Coumarins and their derivatives:

Coumarins and their derivatives possess a wide range of pharmaceutical actions and biological functions and play a vital role in drug discovery. The hepatoprotective activity of coumarin and its derivatives, such as esculetin, scoparone, and 4methylumbelliferone, were explored. Initially, male Sprague-Dawley rats are treats with coumarins and their derivatives. The esculetin and scoparone were given orally at the dose of (35 mg kg^{-1}). It prevented CCl_4-induced hepatotoxicity, and decrease in MDA levels, and an increase in SOD and CAT. In comparison, 4-methylumbelliferone (35 mg kg^{-1}) and coumarin (30 mg kg^{-1}) did not affect carbon tetrachloride (CCl_4) induced hepatotoxicity. Based on the reported data, esculetin and scoparone have protective activity, indicating that coumarins chemical structures prevent oxidative stress (Atmaca *et al*., 2011).

Quercetin:

Quercetin is a (2-(3,4-dihydroxy phenyl)-3,5,7-trihydroxy-4H-chromen-4-one). One of the most abundant flavonoids reported for its wide range of pharmacological properties. The research studies related to biochemical and molecular mechanisms involved in quercetin's hepatoprotective activity. Quercetin exhibited hepatoprotective activity against certain chemicals such as 2-butoxyethanol, paracetamol, acrylamide, etc. Pretreatment is done with quercetin (70 mg/kg/day/6 weeks) and the co-administration of acrylonitrile. It prevented acrylonitrile-induced modifications in the hepatic system (Pingili *et al*., 2019; Salem *et al*., 2011). Histopathological findings supported the biochemical results. The reported data suggest that quercetin possesses hepatoprotective activity. Quercetin lowered the ALT, AST, LDH, and TOS levels while it increases GSH-Px, SOD, and TAS levels. Also, lipid profile changed with quercetin. These data revealed that elevated oxidative stress in the liver of metabolic syndrome was reduced by quercetin (Faras *et al*., 2017; Bilginoglu, 2019).

Rutin:

Rutin is a (3, 3′, 4′, 5, 7-pentahydroxyflavone-3-rhamnoglucoside). It is an important flavonoid also known as vitamin P and quercetin-3-*O*-rutinoside. The investigated studies gave evidence for hepatoprotective activity on cholestatic liver injury. The studies conducted on the redox-sensitive intracellular signaling molecule extracellular signal-regulated kinase (ERK) demonstrated an inhibitory effect of rutin. It also attenuated BDL-induced reduction in heme oxygenase-1 (HO-1), NF-E2-related factor 2 (Nrf2), and AMP-activated protein kinase (AMPK). The antioxidative and anti-inflammatory effects show the beneficial effects of rutin. *Rutin* is an active constituent that acts as gastroprotective, hepatoprotective, and anti-diabetic (Pan *et al*., 2014).

Silymarin:

Silymarin is a flavonolignan used as a hepatoprotective agent. Silymarin shows hepatoprotective activity against paracetamol-induced lipid peroxidation and liver damage. Silymarin and its most active known constituent silibinin, have been reported against various epithelial cancers, namely skin, colon, liver, and lung (Muriel *et al*., 1992; Papackova *et al*., 2018; Bektur *et al*., 2013).

Isoorientin:

Isoorientin (3', 4', 5, 7-tetrahydroxy-6-C-glucopyranosyl flavones), a natural *C*-glucosyl flavones, has broad pharmacological activities that generate interest in the research field. The study of hepatoprotective activity of Isoorientin (15 mg per kg body weight) exhibited a significant effect. Another study was conducted in C57BL/6J mice to evaluate the Isoorientin *in-vivo* and HepG2 cells' hepatoprotective effect. The study shows that 50mg of Isoorientin significantly reduced APAP-induced hepatotoxicity. These effects accompanied by reduction of malondialdehyde (MDA) formation and myeloperoxidase level (MPO) and by decreased superoxide dismutase (SOD) and glutathione (GSH) depletion (Orhan *et al*., 2003; Fan *et al*., 2018).

Andrographolide:

Andrographolide, 3-[2-{decahydro-6-hydroxy-5-(hydroxymethyl)-5,8*a*-dimethyl-2-ethylene-1-naphthalenyl} ethylidene]dihydro-4-hydroxy, 2(3*H*)-furanone is a major active diterpenoid lactone.

The reported data suggested that the andrographolide acts as hepatoprotective against paracetamol-induced hepatotoxicity in mice (Kapil *et al*., 1993; Handa *et al*., 1990).

The secondary metabolites like flavonoids, lignans, phenolic compounds, etc., have been reported for hepatoprotective activity. The combination of phytoconstituents also acts as hepatoprotective agents. Some are reported for their activity—for example, rutin and quercetin, curcumin and silymarin, etc., against various hepatotoxicity-induced chemicals and liver damage (Domitrovic *et al*., 2012; Shi *et al*., 2014; Sameh, 2016).

Table 1: *In-vivo* studies conducted to determine the hepatoprotective activity of chemical constituents

Compounds	Dose and Animal model	Reference
Embelin	50mg and 100mg/kg body weight on N-Nitrosodiethylamine and carbon tetrachloride induce preneoplasia and toxicity in rat liver.	Poojari *et al*. (2010)
	They administered embelin via an intragastric gavage at 50ug/g body weight of mice from TAA-induced acute liver injury.	Wang *et al*. (2019)
	25mg/Kg body weight of embelin on lipid peroxidation and free radical scavenging activity against liver damage in rats.	Singh *et al*.(2009)
Curcumin	75 mg kg^{-1} to male wistar rats	Nanji *et al*. (2003)
	Curcumin acts as hepatoprotective against heavy metals-induced liver damage.	Garcia Nino *et al*. (2014)
	The orally administered curcumin (80 mg/kg body wt.) has shown the protective effect against the hepatotoxicity induced by chloroquine phosphate in Swiss albino male mice.	Dattani *et al*. (2010)
	Administration of (100mg/kg, I.P.) curcumin acts against the methotrexate-induced hepatic oxidative damage in rats.	Hemeida *et al*. (2008)
	↓ALT, ↓AST, ↓ALP, ↓LDH, ↓GGT	Nabavi *et al*. (2013)
Coumarin and its derivatives	(30 mg kg^{-1}) administered orally with an intragastric cannula in Male Sprague–Dawley rats (150–200 g).	Atmaca *et al*. (2012)
Rutin	100 mg kg^{-1} ↓ALP, ↓ALT, ↓AST	Sintayehu *et al*. (2012)
	Oral administration of rutin has shown protective effects on liver injury induced by biliary obstruction in rats.	Pan *et al*. (2014)
Isoorientin	15 mg kg^{-1} ↑tissue GSH, ↓ALT,↓AST	Orhan (2003).
	50 mg kg^{-1} Isoorientin ameliorated APAP-induced hepatotoxicity by activating Nrf2 via the AMPK/Akt/GSK3b pathway.	Fan *et al*. (2018)
Quercetin	Protective effect of quercetin (15mg/kg/day, administered by gavage) against oxidative stress in the liver from metabolic syndrome rats.	Bilginoglu (2019)
	50mg/kg body weight (b.w.) administered orally to determine the hepatoprotective activity of quercetin against paracetamol-induced liver toxicity in rats.	Faras *et al*. (2017)
	(70mg/kg/day/6 weeks) quercetin has shown hepatoprotective activity against acrylonitrile-induced hepatotoxicity in rats.	Salem *et al*. (2011)
Silymarin	200mgkg^{-1} of silymarin administered orally to protects against Paracetamol-induced lipid peroxidation and liver damage.	Muriel *et al*. (1992)
	100mg/kg of silymarin shows protective effects against acetaminophen-induced hepatotoxicity and nephrotoxicity in mice	Bektur *et al*. (2013) & Papackova *et al*. (2018)
Andrographolide	(100 mg/kg, *i.p*.) ↓ CCl_4 or tBHP induced hepatic toxicity in serum MDA, GPT, ALP contents in mice.	Kapil *et al*. (1993)
	(100 mg/kg) ↓ paracetamol-induced hepatotoxicity in mice.	Handa and Sharma, (1990)

Table 2: *In-vitro* studies of some compounds

Compounds	Dose and observation	Reference
7-*O*-[2-*O*-(5-*O*-Vanilloyl-β-Dapiofuranosyl)-β-D-glucopyranosyl]-phenyl methanol	1×10^{-5} M ↑Cell survival (WB-F344 cells) ↑Inhibition of cytotoxicity	Feng *et al*. (2014)
1-*O*-[6-*O*-(5-*O*-Vanilloyl-β-Dapiofuranosyl)-β-D-glucopyranosyl]-3,4,5 trimethoxybenzene	1×10^{-5} M ↑Cell survival (WB-F344cells) ↑Inhibition of cytotoxicity	Feng *et al*. (2014)
1-*O*-[2-*O*-(5-*O*-Syringoyl-β-Dapiofuranosyl)-β-D-glucopyranosyl]-Isoamyl alcohol	1×10^{-5} M ↑Cell survival (WB-F344 cells) ↑Inhibition of cytotoxicity	Feng *et al*. (2014)
Hydrangeside A	10 Mm ↑Cell survival (HL-7702 cells) ↑Inhibition of cytotoxicity	Shi *et al*. (2014)
Hydrangeside C	10 μM ↑Cell survival (HL-7702 cells) ↑Inhibition of cytotoxicity	Shi *et al*. (2014)

Hydrangeside D	10 µM ↑Cell survival (HL-7702 cells) ↑Inhibition of cytotoxicity	Shi *et al*. (2014)
Onitin	1, 10, 50and 100 µM EC_{50} of 85.8 mol L^{-1} in HepG2 cells	Oh *et al*. (2004)
5-*O*-Caffeoylquinic acid	0.39 mmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)
5-*O*-(*E*)-*p*-Coumaroylquinic acid	0.39 mmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)
Gallic acid	10–20 mg kg^{-1} ↑SOD, ↑CAT,↑GSH, ↓TBARS, ↓ALP, ↓AST, ↓ALT, ↓TB, ↓glucose, ↓triacylglycerol, ↓cholesterol ↑protein, ↑Alb, ↑lipase,↑α-amylase	Nabavi *et al*. (2013)
3-*O*-Caffeoylquinic acid	0.39 mmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)
3,4-Di-*O*-caffeoylquinic acid	0.39 mmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)
3,5-Di-*O*-caffeoylquinic acid	0.39 mmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)
3,5-Di-*O*-Caffeoyl*muco*-quinic acid	0.39 mmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)
4,5-Di-*O*-caffeoylquinic acid	0.39 mmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)
4-{Erythro-2-[3-(4-hydroxyl-3,5-dimethoxyphenyl)-3-*O*-β-Dglucopyranosylpropan-1-ol]}-*O*syringaresinol	1 × 10−5 mol L^{-1} ↑Cell survival (WB-F344 cells) ↑Inhibition of cytotoxicity	Feng *et al*. (2014)
Phyllanthin	10–30 µmol L^{-1} ↓ALT, ↓LDH, ↓MDA, ↑GSH, ↑cell viability on HepG2 cells	Krithika *et al*. (2009).
Quercetin 5-*O*-β-Dglucopyranoside	390 µmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)
Quercetin 3-*O*-a-Lrhamnopyranosyl (1→6)-β-Dglucopyranoside	390 µmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)
5,2′-Dihydroxy-7-*O*-β- D-glucuronyl flavone	390 µmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)
Luteolin	1, 10, 50 and 100 µmol L^{-1} EC_{50} of 20.20 µmol L−1 in Hep G2 cells	Oh *et al*. (2004)
Luteolin 7-*O*-β-Dglucuronide	390 µmol L^{-1} ↑Inhibition of HBV secretion from HepG2.2.15 cells ↑Inhibition of HBV DNA replication or transcription	Kim *et al*. (2007)

CONCLUSION

In this review, natural products with exogenic antioxidant effect and adequate hepatotoxic potential data compiled. The current research on natural products focuses on their positive correlation with liver damage reduction either in *in-vivo* or *in-vitro* models. These studies revealed relevant effectiveness in protecting liver tissues (*in vivo*), preserving liver histopathology, lowering liver enzymes' activity (*in vitro*), and increasing the viability of normal liver cells. The results reinforce the idea that natural sources of bioactive compounds can be a solution for treating liver diseases.

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REFERENCE

Anonymous. Hepatitis B, World Health Organization, https://www.who.int/news-room/fact-sheets/detail/hepatitis-b. (2020).

Atanasov, A.; Zotchev, S.; Dirsch, V. and Supuran, C. (2021). Natural products in drug discovery: advances and opportunities, *Nature Reviews Drug Discovery*. 20: 201-216.

Atmaca, M.; Bilgin, H.; Obay, B.; Diken, H.; Kelle, M. and Kale, E. (2011). Hepatoprotective effect of coumarin and coumarin derivatives on carbon tetrachloride-induced hepatic injury by antioxidative activities in rats, *Journal of Physiology and Biochemistry*. 67: 569.

Bektur, E.N.; Sahin, E.; Baycu, C. and Unver, G. (2013). Protective effects of silymarin against acetaminophen-induced hepatotoxicity and nephrotoxicity in mice, *Toxicology and Industrial Health.* 32: 589-600.

Bilginoglu, A. (2019). Possible protective effect of quercetin against oxidative stress in liver from metabolic syndrome rats*, J Contemp Med.* 9(3): 203-208.

Dattani, J.J. Rajput, D.K.; Moid, N.; Highland, H.N.; George, L.B. and Desai, K.R. (2010). Ameliorative effect of curcumin on hepatotoxicity induced by chloroquine phosphate, *Environ Toxicol Pharmacol*. 30(2): 103– 9.

Domitrovic, R.; Jakovac, H.; Marchesi, V.; Knezevic, S.; Cvijanovic, O.; Tadic, Z.; Romic, Z. and Rahelic, D. (2012). Differential hepatoprotective mechanisms of rutin and quercetin in CCl_4-intoxicated BALB/cN mice, *Acta Pharmacol Sin.* 33(10): 1260–1270.

Fan, X.; LV, H.; Wang, L.; Deng, X. and Ci, X. (2018). Isoorientin Ameliorates APAP-Induced Hepatotoxicity via Activation Nrf2 Antioxidative Pathway: The Involvement of AMPK/Akt/GSK3b, *Frontiers in Pharmacology*. 9.

Faras, A. and Elsawaf, A. (2017). Hepatoprotective activity of quercetin against paracetamol-induced liver toxicity in rats, *Tanta Med. J.*45: 92-98.

Feng, Z.; Song, S.; An, Y.; Yang, Y.; Jiang, J. and Zhang, P. (2014). Hepatoprotective acyl glycosides obtained from *Erycibe hainanesis*, *Phytochem Lett.* 9: 163–167.

Garcia-Nino, W.R. and Pedraza-Chaverrí, J. (2014). Protective effect of curcumin against heavy metals-induced liver damage, *Food Chem. Toxicol*. 69: 182–201.

Gupta, O.P.; Ali, M.M.; Ray Ghatak, B.J. and Atal, C.K. (1977). Some pharmacological investigations of embelin and its semisynthetic derivatives, *Indian J Physiol Pharmacol*. 21: 31-9.

Handa, S.S. and Sharma, A. (1990). Hepatoprotective Activity of Andrographolide from *Andrographis paniculata* against carbontetrachloride, *Indian J Med Res.* 92, 276-283.

Hemeida, R.A. and Mohafez, O.M. (2008). Curcumin attenuates methotraxate induced hepatic oxidative damage in rats, *J Egypt Natl Cancer Inst.* 20(2): 141– 8.

Kang, S.; Sung, S.; Park, J. and Kim, Y. (1998). Hepatoprotective activity of scopoletin, a constituent of *Solanum lyratum*, *Archives of Pharmacal Research*. 21: 718-722.

Kapil, A.; Koul, I.B.; Banerjee, S.K. and Gupta, B.D. (1993) Antihepatotoxic Effects of Major Diterpenoid Constituents of *Andrographis paniculata*, *Biochemical Pharmacology.* 46(1): 182-185.

Khana, H.; Ullaha, H. and Nabavib, S. (2019) Mechanistic insights of hepatoprotective effects of curcumin: Therapeutic updates and future prospects, *Food and Chemical Toxicology*. 124: 182–191.

Kim, K.H.; Kim, Y.H. and Lee, K.R. (2007). Isolation of quinic acid derivatives and flavonoids from the aerial parts of *Lactuca indica* L. and their hepatoprotective activity in vitro, *Bioorg Med Chem Lett.* 17: 6739–6743.

Krithika, R.; Mohankumar, R.; Verma, R.J.; Shrivastav, P.S.; Mohamad, I.L. and Gunasekaran, P. (2009). Isolation, characterization and antioxidative effect of phyllanthin against CCl_4-induced toxicity in $HepG_2$ cell line, *Chem. Biol. Interact.* 181: 351–358.

llyas, U.; Katare, D.; Aeri, V. and Naseef, P. (2016). A review on hepatoprotective and immunomodulatory herbal plants, *Pharmacognosy Reviews*. 19(10): 66.

Muriel, P.; Garciapina, T.; Alvarez, P.V. and Mourelle, M. (1992). Silymarin protects against paracetamol induced lipid peroxidation and liver damage, *J Appl Toxicol*. 12(6): 439-442.

Nabavi, S.; Habtemariam, S.; Daglia, M.; Sureda, A.; Moghaddam, A.; Nabavi, S. and Amani, M. (2013). Curcumin and liver disease: from chemistry to medicine, *Comprehensive reviews in food science and food safety*. 13: 62-77.

Nabavi, S.F.; Nabavi, S.M.; Habtemariam, S.; Moghaddam, A.H.; Sureda, A. and Jafari, M. (2013). Hepatoprotective effect of gallic acid isolated from *Peltiphyllum peltatum* against sodium fluoride-induced oxidative stress, *Ind Crop Prod.* 44: 50–55.

Nanji, A.; Jokelainen, K.; Tipoe, G.L.; Rahemtulla, A.; Thomas, P. and Dannenberg, A.J. (2003). Curcumin prevents alcohol-induced liver disease in rats by inhibiting the expression of NF-κB-dependent genes, *Am J Physiol Gastrointest Liver Physiol*. 284: G321–G327.

Oh, H.; Kim, D.H.; Cho, J.H. and Kim, Y.C. (2004). Hepatoprotective and free radical scavenging activities of phenolic petrosins and flavonoids isolated from *Equisetum arvense*, *J Ethnopharmacol.* 95: 421–424.

Orhan, D.D.; Aslan, M.; Aktay, G.; Ergun, E.; Yesilada, E. and Erguna, F. (2003). Evaluation of hepatoprotective effect of *Gentiana olivieri* herbs on subacute

administration and isolation of active principle, *Life Sci.* 72: 2273–2283.

Pan, P.H.; Yilin, S.; Yuwang, Y.; Ying Chen, W.; Hanchuang, Y.; ChengWu, C. and JungChen, C. (2014). Protective effects of rutin on liver injury induced by biliary obstruction in rats, *Free Radic Biol Med.* 73: 106-116.

Papackova, Z.; Heczkova, M.; Dankava, H.; Sticova, E.; Lodererova, A.; Bartonova, L.; Poruba, M. and Cahova, M. (2018). Silymarin prevents acetaminophen-induced hepatotoxicity in mice, *PLOS ONE.*13.

Pereira, C.; Barros, L. and Ferreira, I. (2016) Extraction, identification, fractionation and isolation of phenolic compounds in plants with hepatoprotective effects, *J Sci Food Agric.* 96: 1068–1084.

Pingili, R.B.; Challa, S.R.; Pawar, A.K.; Toleti, V.; Kodali, T. and Koppula, S. (2019). A systematic review on hepatoprotective activity of quercetin against various drugs and toxic agents: Evidence from preclinical studies, *Phytother Res.* 34: 5-32.

Poojari, R.; Bhagwat, S.; Gupta, S.; Maru G. and Khade, B. (2010). Chemopreventive and hepatoprotective effects of embelin on N-nitrosodiethylamine and carbon tetrachloride induced preneoplasia and toxicity in rat liver, *Asian Pacific Journal of Cancer Prevention*. 11: 1015-1020.

Salem, O.; Ellah, M. and Ghonaim, M. (2011). Hepatoprotective activity of quercetin against acrylonitrile-induced hepatotoxicity in rats, *J Biochem Mol Toxicol.* 25: 386-92.

Sameh, S.D. (2016) Silymarin and Curcumin has a Potential Hepatoprotective Effect against Chemically-Induced Liver Dysfunction, *Virology & Immunology Journal*. 1 (1).

Shi, J.; Li, C-J.; Yang, J-Z.; Ma, J.; Wang, C. and Tang, J. (2014). Hepatoprotective coumarins and secoiridoids from *Hydrangea paniculata, Fitoterapia.* 96: 138–145.

Singh, D.; Singh, R.; Singh, P. and Gupta, R.S. (2009). Effects of Embelin on lipid peroxidation and free radical scavenging activity against liver damage in rats, *Basic Clin. Pharmacol. Toxicol*. 105: 243-248.

Sintayehu, B.; Bucar, F.; Veeresham, C. and Asres, K. (2012). Hepatoprotective and free radical scavenging activities of extracts and a major compound isolated from the leaves of *Cineraria abyssinica* Sch. Bip. ex A. Rich, *Pharmacogn J.* 4: 40–46.

Sumeet, K.A.; Harshad, D.; John, E. and Patrick, S.K. (2019). Burden of liver diseases in the world, *Journal of hepatology*. 70(1): 151-171.

Wang, H.; Zhang, H.; Wang, Y.; Yang, L. and Wang, D. (2019). Embelin can protect mice from thioacetamide-induced acute liver injury, Biomedicine & Pharmacotherapy. 118: 1093602.