Advances in Bioresearch
Adv. Biores., Vol 14 (1) January 2023: 75-81

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.14.1.7581

Advances in Bioresearch

REVIEW ARTICLE

Effect of Plant Phytochemicals against Hepatotoxicity: A Review

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ABSTRACT
One of the largest organs in a mammalian body, the Liver serves a variety of purposes. The fact that the liver's activity cannot be replaced by artificial technology, despite intensive efforts, demonstrates its unique role. The liver is involved in the maintenance of the organism's homeostasis, and many important biochemical events in the human body, such as biomolecule synthesis and detoxification, take place here. Therefore, any damage or injury to the liver can lead to many fatal implications such as the necrosis of hepatocytes, fibrosis, decrease in lipid peroxidation, increase in glutathione levels and oxidative changes. Traditional medicine derived from plants has been used globally since years. The World Health Organization (WHO) has reported that nearly 80% of the total population in developing countries like India depends on medicines obtained from plants. In recent years, there has been a surge in the search and usage of medications and dietary supplements derived from plants, and a number of individuals with liver problems have used these as botanicals. The hepatoprotective role of many medicinal herbs used to treat liver diseases have been documented since the 16th century. The hepatoprotective role of these herbs is devoted to the antioxidant, anti-inflammatory and antiapoptotic properties. Through the present review, an attempt has been made to present a broad and thorough database of information regarding the hepatoprotective role of potent phytochemicals present in medicinal plants.
Keywords: *phytochemicals, hepatoprotective, anti-inflammatory, antioxidant, medicinal*

Received 14.10.2022 Revised 12.11.2022 Accepted 19.12.2022

How to cite this article:
Tejinder K C, Reena V, Priyanka M. Effect of Plant Phytochemicals against Hepatotoxicity: A Review. Adv. Biores. Vol 14 [1] January 2023.75-81

INTRODUCTION

Liver, the most important organ of the human body, is the primary site for metabolism of xenobiotics. It plays a crucial role in transforming toxic chemicals into intermediate compounds, such as the free radicals, which have the potential to alter structure and function of cellular macromolecules. Any injury or impairment of liver or its functions may lead to serious implications on human health [1].

Hepatic damage is linked to changes in the metabolic processes of the liver, necrosis at cellular level, increased lipid peroxidation and depletion of glutathione levels. An elevation in the levels of biochemical markers such as transaminases, alkaline phosphatase, triglycerides and cholesterol is also reported in liver diseases [2].

The chemicals which are potent enough to cause liver injury are called as hepatotoxicants, and include chemicals such as *N*-nitrosodimethylamine, hydrazine and carbon disulfide. These chemicals can come directly from food, such as mushrooms and fruits, having hepatotoxin, or they can be generated during food processing, such as polycyclic aromatic hydrocarbons. Environmental toxicants such as inorganic elements also have the potential to cause liver injuries. For example, exposure to Beryllium causes liver necrosis in the middle zone of the liver.

One of the most cited reasons for withdrawal of any drug from the market is the adverse effects to the liver. Drug induced hepatotoxicity is thought to account for nearly 5% of daily hospital admissions [3]. There are few treatment options for liver diseases, and the medicinal drugs lack efficacy, are costly and carries the risk of adverse effects [4]. So there is a need for effective therapeutic agents with minimal side effects for treating liver diseases. Plants potentially constitute such groups, which can be used as hepatoprotective agents.

Over the last few years, the usage of herbal extracts and other plant derived products have enormously increased and their safety and efficacy for treating hepatotoxicity appears to be favorable. There are many plant extracts like that of *Andrographis paniculata*, *Ocimum sanctum*, *Solanum nigrum*, *Silybum marianum* and *Phyllanthus niruri* which are scientifically proven to possess hepatoprotective roles [5].

Phytochemicals are naturally occurring bioactive compounds present in plants. They protect the plant from a variety of diseases and add colour, aroma, and flavor to them. In general, they can be defined as naturally occurring chemicals that are derived from plants and provide protection against various hazardous toxins. These show hepatoprotective roles mainly due to their antioxidant effect but there are many other effects also such as immunomodulatory, antiviral and anti-inflammatory which are responsible for the protective nature.

The use of herbal drugs for treating liver disorders is an ancient method of medicine, but now with advancements in research it is included as complementary and alternative medicine for treatment and prevention of liver diseases. Several hundred plants and the phytochemicals extracted from them have been reported for their effectiveness in the management of liver diseases and the results have shown that these offer hepatoprotection by mitigating the toxic effects of the hepatotoxic agents. Several formulations of single plant extract or numerous polyherbal formulations are now available for treating the signs of hepatotoxicity [6]. Some polyherbal or single herb formulations readily available in the market to treat hepatotoxicity are Silymarin, Milkthistle, Liv 52®, D-003®, Kava herbal dietary supplements, and Shekwasha.

Therefore, this review provides an overview of plant derived compounds, or phytochemicals that have been found useful in the treatment of hepatotoxicity. The phytochemicals listed in the review have been found to reduce liver injury both in *in vitro* and *in vivo* liver toxicity models. Therefore, such Phytochemicals have been discussed in greater depth, with an emphasis on their source, chemical name and their mechanism of countering liver toxicity.

Acanthoic Acid

Acanthoic acid belongs to the category of diterpene and is extracted from the bark of *Acanthopanax koreanum* Nakai, family Arialaceae. Since time immemorial it is traditionally used to treat rheumatism, diabetes and hepatitis [7]. Wu *et al.,* in [40] elaborated that pretreating the liver tissues with Acanthoic acid improved the antioxidants levels and inhibited the mechanism of peroxidation of lipid. Furthermore, it also inhibits apoptosis by ameliorating the hypoxia-inducing factors and caspases.

Yao e*t al.,* [42] documented that oral administration of Acanthoic acid in mice increased the AST, ALT, ALP and LDH levels and also, reduced the accumulation of fat droplets in the liver. Further, it prevented alcohol-induced lipid deposition and inflammation by regulating liver kinases and receptors present in the liver.

Amyrin

Amyrins are triterpenes found in various plant materials such as the leaves, bark, wood, and resins of medicinal plants of several species of the *Burseraceae* family. The three isomers of Amyrin which occur naturally are α-amyrin, β-amyrin and δ-amyrin. Amyrin isomers are known for their hepatoprotective action by restoring enzymes and glutathione (GSH) levels of the liver. It also reduces the histopathological alterations and the mortality in a manner similar to N-acetylcysteine [8].

Furthermore, the role of Amyrin as a hepato modulator against the hepatic oxidative stress caused by Carbon tetrachloride (CCl_4) [9]

Anthocyanin

Anthocyanins are water-soluble coloured pigments present in plants that belong to the phenolic class of phytochemicals and are well known for their hepatoprotective role against various toxicants. The anthocyanins from *Hibiscus sabdariffa* provide protection against the Acetaminophen-induced hepatotoxicity in the male mice and improve the levels of liver enzymes [10].

Administration of the purple-fleshed sweet potato anthocyanins to mice restored the liver enzymes, improved the antioxidant enzyme levels, inhibited peroxidation of lipids and diminished the GSH depletion from the mice liver [11]. Besides this, the anthocyanin rich extract of the black rice bean are also known to significantly decrease the serum levels of the liver enzymes such as the ALT, Superoxide dismutase (SOD) and Glutathione (GSH) increased due to the CCl_4 intoxication [12].

Berberine

Berberine, is an alkaloid that is obtained from the dietary plants, such as *Berberis aristata*. It is well known for its pharmacological, antimicrobial, antiviral, anti-inflammatory, hepatoprotective and anticancerous activities. The hepatoprotective role of Berberine was demonstrated by Janbaz and Gilani [18], against the Acetaminophen (APAP) induced hepatotoxicity. Feng *et al.,* [13] demonstrated its protective role against CCl_4 induced toxicity in the liver tissues.

It was observed that both pre- and post treating with doses of Berberine significantly reduced serum ALT and AST activities in a dose-dependent approach and lowered liver damage. Berberine was also reported to reduce mortality, restore levels of liver enzyme and inhibits the components of inflammasomes which are major mediator of inflammation requiring activation of cytokines that are generated upon the activation of caspase-1 in APAP induced hepatotoxicity [14].

Carvacrol

Carvacrol, is a polyphenolic monoterpenoid that is present in the essential oils of many herbs such as the Oregano (*Origanum vulgare*), Wild bergamot (*Citrus aurantium* bergamia), Thyme (*Thymus vulgaris*) and Pepperwort (*Lepidium flavum*) *etc.* It possesses several bioactive properties such as antimicrobial, antitumorous, anti-mutagenic, anti-inflammatory, Acetylcholinesterase inhibitor and antihepatotoxic. It also aids in hepatoprotection against various hepatotoxicants. The hepatoprotective property of Carvacrol against the D-galactosamine-induced hepatotoxicity in rats. Administration of carvacrol reduced elevated levels of liver enzymes and antioxidants. The results were also supported by the normal histology of the liver tissues [16]. Carvacrol was also reported to suppress the expression of the inflammatory marker genes such as TNF-α, IL-6,COX-2 and NF-κB in the liver tissues. Besides this Carvacrol role in hepatoprotection against N-nitrosodiethylamine induced liver injury [15] has also been documented.

Curcumin

Curcumin, is a yellow-coloured poly phenolic constituent present in rhizomes of *Curcuma longa*, commonly known as Turmeric. Curcumin possesses several health benefits. It has been shown to possess an anti-inflammatory properties and helps in the management of degenerative eye conditions. Therefore, it is considered “nature's medicine”. Most of the therapeutic benefits possessed by Curcumin are due to antioxidant and anti-inflammatory activities [17].

The ameliorative effect of Curcumin against sodium-fluoride-induced hepatotoxicity indicated that Curcumin reduced the fluoride-induced abnormalities in serum biochemistry factors such as ALP, ALT, AST, total protein and albumin levels. These enzymes together protected the rat liver against the antioxidant enzyme imbalance and also reduced the peroxide levels [18]. The ameliorative effect of curcumin against lead acetate induced hepatotoxicity and haemato-biochemical alterations in rats [19].

Epigallacatechin-3-gallate

Epigallacatechin-3-gallate, is a polyphenolic constituent and is an important catechin that present in several plants such as green tea and the black tea. It is known for its numerous pharmacological and therapeutic properties i.e., hepatoprotective, anticancerous, antiinflammatory, free radical scavenging and antioxidant.

Studies have shown that it possesses hepatoprotective activity against chemically induced liver injuries [20]. Mice treated with Epigallacatechin-3-gallate have shown reduced biochemical DNA damage, antioxidant levels and pathological changes in the liver tissues [21]. It is also documented to curb the toxicity of APAP-induced hepatotoxicity by restoring the liver enzyme levels and suppressing activities of hepatic cytochromes and enzymes uridine diphosphate glucuronosyltransferase and sulfotransferase in the hepatocytes of rat liver [39].

Gallic Acid

Gallic Acid, is a polyphenolic secondary metabolite present in different parts of the plants such as the leaves, bark, fruits, seeds, and wood. They are present in different concentrations in fruits and nuts such as blueberry, blackberry, strawberry, grapes, plum, mango, hazelnut *etc.* It is found in a free and combined state with tannins as gallotannins. Studies have reported its capability in regulating several biological activities: antibacterial, antiviral, anti-cancerous, anti-inflammatory, cardio-protective and hepatoprotective [22].

The hepatoprotective role of Gallic acid in restoring the liver enzymes and inhibiting the pro-inflammatory cytokines. Mice fed with fruits rich in gallic acid have been observed to have better integrity of hepatic membranes [23]. The liver and bile duct enzymes also improved and the efficacy of the hepatic antioxidant enzymes uplifted on administration of Gallic acid [24].

Geranylgeranylacetone

Geranylgeranylacetone, is a polyisoprenoid known for its anti-cancerous properties. It has been observed that it ameliorates the necrosis of the liver cells by inhibiting the activities of lipid peroxidase and myeloperoxidase; and by restoring the liver enzymes. [25].

Xanthophylls

Lutein, Zeaxanthin and Meso-Zeaxanthin are three Xanthophyll concentrate carotenoids of the human macula. Lutein and Zeaxanthin concentrates are obtained from green vegetables, but Meso-Zeaxanthin is almost absent in food sources. Meso-Zeaxanthin is produced at the region macula of the human eye by the conversion of the ingested carotenoids and is known to be an essential nutrient for the health of human eyes. The three xanthophylls besides providing protection against chronic eye conditions also give protection against cardiovascular diseases, strokes and eye diseases such as age-related macular degeneration and cataract. [26].

Firdous *et al*., 2011 documented that Meso-Zeaxanthin normalizes the levels of serum GSH levels and restores the liver enzymes which were affected due to APAP hepatotoxicity. The potent use of dietary Lutein in treating liver diseases. The study observed that Lutein improved the activities of the antioxidant enzymes and increased the mRNA and protein expression in the mice suffering from Arsenic induced toxicity via Nrf 2 Signaling [27].

Quercitin

Quercitin, one of the most popular flavonoid compounds and a potent antioxidant agent, is present in a variety of plants. The hepatoprotective role of Quercitin has been documented in rat models and its role is known to provide protection against induced liver injuries. Besides being a hepatoprotective agent, it also acts as an effective treatment of cancer, cardio-vascular and renal diseases.

There are reports that the oral intake of Quercitin protects the liver against ischemia and reperfusion injuries [28].

Upon administration with quercitin Bona *et al*., 2012, reported significant decrease in elevated serum levels of AST and ALT in the rats intoxicated with CCl_4, supporting the hepatoprotective role of Quercitin. The administration of quercetin also causes a significant reduction in biochemical alterations, thus increasing the survivability in animals. By the restoration of liver enzymes Quercitin ameliorates APAP-induced hepatotoxicity and inhibits liver peroxidation [29].

Rutin

Rutin, chemically known 3,3',4',5,7-pentahydroxyflavone-3-rhamnoglucosid, is a polyphenolic flavonoid belonging to the class flavanols of the flavonoids and is abundantly found in various fruits such as cherries, grapes, plums and oranges. One of the best dietary sources of Rutin is *Fagopyrum esculentum* popularly known as Buckwheat. Rutin has various pharmacological properties such as antimicrobial, anti-inflammatory, anti-allergic and antihypertensive [30]. The hepatoprotective role of Rutin was due to it having antioxidant, anti-inflammatory and organ protection properties in many animal studies. Rutin have been documented to restore the levels of liver enzymes and reduce mortality in mice intoxicated with CCl_4 and paracetamol [19]. Rutin has also been associated with reducing the triglyceride levels and ameliorating the oxidative injuries in the fat-enriched hepatocytes in the mouse model of non-alcoholic fatty liver. It also represses autophagic function of the tissues of the liver by downregulation of the key autophagy markers [32].

Tannic Acid

Tannic acid, a specific type of tannin, is a polyphenolic compound that is abundantly found in several fruits, vegetables, beverages *e.g.,* strawberries, grapes, beans, coffee, cocoa and nuts. Tannic acid possesses several activities such as it acts as an antioxidant, anti-inflammatory and anti-apoptotic. It has been documented to provide hepatoprotection against toxicities like Zhang *et al*., [44] elaborated the tannic acid hepatoprotective potential against the toxicity caused by acetaminophen. Administration of tannins restores the functions of the enzymes of the liver and inhibits the formation of endothelin-1, nitric oxides and malondialdehyde. In CCl_4 induced hepatotoxicity, tannic acid restored the elevated levels of ALT, AST, GSH, SOD and dismutase. Further, it was also reported that tannic acid reduced steatosis degeneration and nodule formation in the liver cells [31].

Thymol

Thymol, is a natural monoterpenoid derivative of cymene found primarily in the herb, Thyme. Due to its nutritional, biological and pharmacological values it has numerous health-promoting and disease-preventing properties. Thymol possesses high antioxidant properties and has shown to alleviate the titanium dioxide nanoparticles liver injuries improving the enzymatic and non-enzymatic antioxidant defense along with histopathological preservation in liver tissues [35]. Geyikoglu *et al*., [15] reported hepatoprotective role of Thymol against the Drug toxicity. Thymol down regulated the levels of TNF-α, eNOS and some hepatic enzymes and upregulated the Prostaglandin E_2 (PGE2) levels.

Thymoquinone

Thymoquinone, is the major bioactive quinone compound present in the seeds of *Nigella sativa*, popularly known as *kali mirch*. The compounds hold excellent pharmacological properties against various diseases

and exhibit anticancerous, anti-inflammatory, antioxidant, hepatoprotective and antimutagenic properties. Nagi *et al.,* [25] reported that Thymoquinone reduced the increased levels of peroxidase and enzymes. It also down regulated the levels of GSH and ALP in APAP-induced hepatotoxicity.
Significant Reduction in the necrosis and size of tumors was reported upon treatment with a combination of thymoquinone and CB-1954. The combination brought the elevated plasma levels of ALT and AST to normal in the liver tissues [35]. In a study, Aycan I.O. *et al.,* [4] showed that thymoquinone, in a dose-dependent manner, provides protection against acetaminophen-induced hepatotoxicity by suppressing elevated liver enzyme levels and liver injury scores in the mice.

CONCLUSION

Natural products, especially plant phytochemicals, can prove to be a promising therapeutic agent and replacement of the drugs in practice owing to the effectiveness, minimal or no side effects and ameliorative properties. The dietary nature is a bonus and gives all the more reason to decline the available drugs that cause toxicity to the human body. Remarkable phytochemicals like curcumin, thymol, catechins, rutins *etc.* are pharmacologically tested against treatment of liver diseases but still the present data is speculative for therapeutic usage, it could be further useful for the testing of phytochemicals in the clinical settings if their human safety is established.
The pandemic years in India have witnessed a boom in the usage of herbal remedies, along with a renewal of interest in communities to further explore the therapeutic properties of medicinal plants. After the outbreak of Covid the sales and formulations of plant-based drugs have exponentially increased.
The phytochemicals evaluated until now are generally non-toxic in nature; still a few studies regarding toxicity with repeated doses of phytochemicals are highlighted [8]. So, the appropriate selection of plant-based drugs becomes obligatory.
It is envisaged from the present review that plant-based drugs will reduce the risk of hepatotoxicity and will furnish a substitute that can be used for treating many liver diseases.

REFERENCES

1. Abdelhamid FM, Mahgoub HA and Ateya AI (2020). Ameliorative effect of curcumin against lead acetate–induced hemato-biochemical alterations, hepatotoxicity, and testicular oxidative damage in rats. *Environ Sci Pollut Res.,* **27**:10950–10965. Doi: 10.1007/s11356-020-07718-3.
2. Ali BH, Mousa HM and El-Mougy S (2003). The effect of a water extract and anthocyanins of hibiscus sabdariffa L on paracetamol-induced hepatoxicity in rats. *Phytother. Res.,* **17**: 56–59. Doi: 10.1002/ptr.1084.
3. Aristatile B, Al-Numair KS, Veeramani C and Pugalendi KV (2009). Effect of carvacrol on hepatic marker enzymes and antioxidant status in D-galactosamine-induced hepatotoxicity in rats. *Fundam Clin Pharmacol.,* **23**:757-765. Doi:10.1111/j.1472-8206.2009.00721
4. Aycan IO, Tufek A, Tokgoz O, Evliyaoglu O, Firat U, Kavak GO, Turgut H and Yüksel MU (2014). Thymoquinone treatment against acetaminophen-induced hepatotoxicity in rats. *Int J Surg.,* **12**: 213-218. Doi: 10.1016/j.ijsu.2013.12.013.
5. Balan R, Rajendran R,Thandavamoorthy P and Thiruvengadam D (2015). Carvacrol attenuates N-nitrosodiethylamine induced liver injury in experimental Wistar rats. *Food Science and Human Wellness.,* **4**: 66-74. Doi: 10.1016/j.fshw.2015.04.002.
6. Howida S and Abou Seif (2016). Physiological changes due to hepatotoxicity and the protective role of some medicinal plants. *Beni-Suef University Journal of Basic and Applied Sciences*., **5**: 134-146. Doi: 10.1016/j.bjbas.2016.03.004.
7. Bona S, Filippin LI, Di Naso FC, De David C, Valiatti B, IsoppoSchaun M, Xavier RM and Marroni NP (2012). Effect of antioxidant treatment on fibrogenesis in rats with carbon tetrachloride-induced cirrhosis. *ISRN gastroenterology*., **2012**: 762920.Doi: 10.5402/2012/762920
8. Bourhia M, Laasri FE, Moussa SI, Ullah R, Bari A, Saeed Ali S, Kaoutar A, Haj Said AA, El Mzibri M, Said G, Khlil N and Benbacer L (2019). Phytochemistry, Antioxidant Activity, Antiproliferative Effect, and Acute Toxicity Testing of Two Moroccan *Aristolochia* Species. *Evid Based Complement Alternat Med.,* **2019**: 9710876. Doi: 10.1155/2019/9710876.
9. Choi JH, Choi CY, Lee KJ, Hwang YP, Chung YC and Jeong HG (2009). Hepatoprotective effects of an anthocyanin fraction from purple-fleshed sweet potato against acetaminophen-induced liver damage in mice. *J. Med. Food.,* **12**: 320–326. Doi: 10.1089/jmf.2007.0691.
10. Mittal DK, Joshi D and Shukla S (2011). Antioxidant and Hepatoprotective Effects of Polygonum bistorta Linn. and Tannic Acid on Carbon Tetrachloride-treated Rats. *International Journal of Pharmagenesis.,* **2**: 23-30. https://www.omicsonline.org/scientific-reports/srep226.php
11. Stickel F and Schuppan D (2007). Herbal medicine in the treatment of liver diseases *Dig Liver Dis*., **39**: 293-304. Doi: 10.1016/j.dld.2006.11.004.

12. Ali FEM, Abo-Youssef AM, Messiha BAS and Hemeda RAM (2015). Protective Effects of Quercetin and Ursodeoxycholic Acid on Hepatic Ischemia-Reperfusion Injury in Rats. *Clin. Pharmacol. Biopharm.,* **3**: 128. Doi: 10.4172/2167-065X.1000128.
13. Feng Y, Siu KY, Ye X, Wang N, Yuen MF, Leung CH, Tong Y and Kobayashi S (2010). Hepatoprotective effects of berberine on carbon tetrachloride-induced acute hepatotoxicity in rats. *Chin Med*., **5**: 33. Doi: 10.1186/1749-8546-5-33.
14. Firdous AP, Sindhu ER and Kuttan R (2011). Hepato-protective potential of carotenoid meso-zeaxanthin against paracetamol, CCl4 and ethanol induced toxicity. Indian J. Exp. Biol., **49**: 44–49.
15. Geyikoglu F, Yilmaz EG, Erol HS, Koc K, Cerig S, Ozek NS and Aysin F (2018). Hepatoprotective Role of Thymol in Drug-Induced Gastric Ulcer Model. *Ann Hepatol.,* **17**: 980-991. Doi: 10.5604/01.3001.0012.7198.
16. Zhaohua H, Peiyou Q, Yan Z, Songhua C and Guixing R (2013). Identification of anthocyanins isolated from black rice (*Oryza sativa* L.) and their degradation kinetics. *Food Research International*., **50**: 691-697.Doi: https://doi.org/10.1016/ j.foodres.2011.07.037.
17. Jafari A, Karimipour M, Khaksar MR and Ghasemnejad BM (2020). Protective effects of orally administered thymol against titanium dioxide nanoparticle-induced testicular damage. *Environ Sci Pollut Res Int.,* 27: 2353-2360. Doi: 10.1007/s11356-019-06937-7.
18. Janbaz KH and Gilani AH (2000). Studies on preventive and curative effects of berberine on chemical-induced hepatotoxicity in rodents. *Fitoterapia*., **71**: 25–33. Doi: 10.1016/s0367-326x(99)00098-2.
19. Janbaz KH, Saeed SA and Gilani AH (2002). Protective effect of rutin on paracetamol- and CCl4-induced hepatotoxicity in rodents. Fitoterapia., **73**: 557–563. Doi: 10.1016/s0367-326x(02)00217-4.
20. Jung MG, Do GM, Shin JH, Ham YM Park, SY and Kwon O (2013). *Acanthopanax koreanum* Nakai modulates the immune response by inhibiting TLR 4-dependent cytokine production in rat model of endotoxic shock. *Nutrition research and practice*., **7**: 460–465. Doi: https://doi.org/10.4162/nrp.2013.7.6.460
21. Kahkeshani N, Farzaei F, Fotouhi M, Alavi SS, Bahramsoltani R, Naseri R, Momtaz S, Abbasabadi Z, Rahimi R, Farzaei MH and Bishayee A (2019). Pharmacological effects of gallic acid in health and diseases: A mechanistic review. *Iranian journal of basic medical sciences*., **22**: 225–237. Doi: https://doi.org/10.22038/ijbms.2019.32806.7897
22. Lahon K and Das S (2011). Hepatoprotective activity of Ocimum sanctum alcoholic leaf extract against paracetamol-induced liver damage in Albino rats. *Pharmacognosy research*., ***3***:13–18. Doi:https://doi.org/10.4103/0974-8490.79110
23. Li S, Ding Y, Niu Q, Xu S, Pang L, Ma R, Jing M, Feng G, Tang JX, Zhang Q, Ma X, Yan Y, Zhang J, Wei M, Wang HX, Li F and Guo S (2015). Lutein has a protective effect on hepatotoxicity induced by arsenic via Nrf2 signaling. *BioMed research international.*, **2015**: 315205. Doi :https://doi.org/10.1155/2015/315205
24. Hajizadeh MA, Nabavi SF, Nabavi SM, Loizzo MR, Roohbakhsh A and Setzer WN (2015). Ameliorative effects of curcumin against sodium fluoride-induced hepatotoxicity. *Progr Nutr*., **17**: 324-30. https://www.mattioli1885journals.c om/index.php/ progressinnutrition/article/view/4059.
25. Nagi MN, Almakki HA, Sayed-Ahmed MM and Al-Bekairi AM (2010). Thymoquinone supplementation reverses acetaminophen-induced oxidative stress, nitric oxide production and energy decline in mice liver. Food Chem. Toxicol., 48: 2361–2365. Doi: 10.1016/j.fct.2010.05.072.
26. Nishida T, Matsura T, Nakada J, Togawa A, Kai M, Sumioka I, Minami Y, Inagaki Y, Ishibe Y, Ito H, Ohta Y and Yamada K (2006). Geranylgeranylacetone protects against acetaminophen-induced hepatotoxicity by inducing heat shock protein 70. *Toxicology.,* **219**: 187-96. Doi: 10.1016/j.tox.2005.11.018.
27. Abdel-Salam OME, Sleem AA, and Shafee N (2014). Hepatoprotective effects of *Cynara* extract and silymarin on carbon tetrachloride-induced hepatic damage in rats. *Comp Clin Pathol.,* **23:** 709–716. Doi: https://doi.org/10.1007/s00580-012-1675-3.
28. Oliveira FA, Chaves MH, Almeida FR, Lima RC, Jr. Silva RM, Maia JL, Brito GA, Santos FA, and Rao VS (2005). Protective effect of alpha- and beta-amyrin, a triterpene mixture from Protium heptaphyllum (Aubl.) March. trunk wood resin, against acetaminophen-induced liver injury in mice. J. Ethnopharmacol., **98**: 103–108. Doi: 10.1016/j.jep.2005.01.036.
29. Dey P, Saha MR, and Sen A (2013). An overview on drug-induced hepatotoxicity.*Asian J Pharm Clin Res*., **6:** 1-4. https://innovareacademics.in/journals/index.php/ajpcr/article/view/253.
30. Patel K, and Patel D (2019). *The Beneficial Role of Rutin, A Naturally Occurring Flavonoid in Health Promotion and Disease Prevention: A Systematic Review and Update*. Academic Press. Cambridge, US. Doi: 10.1016/B978-0-12-813820-5.00026-X.
31. Liu Q, Pan R, Ding L, Zhang F, Hu L, Ding B, Zhu L, Xia Y, and Dou X (2017). Rutin exhibits hepatoprotective effects in a mouse model of non-alcoholic fatty liver disease by reducing hepatic lipid levels and mitigating lipid-induced oxidative injuries. *Int Immunopharmacol.,* **49**: 132-141. Doi: 10.1016/j.intimp.2017.05.026.
32. Qureshi SA, Jahan M, Lateef T, Ahmed D, Rais S, and Azmi MB (2019). Presence of gallic acid and rutin improve the hepatoprotective strength of *Withaniacoagulans*. *Pak J Pharm Sci.,* **32**: 301-308. http://www.pjps.pk/wp-content/uploads/pdfs/32/1/Supplementary/9-SUP-995.pdf
33. Rasool MK, Sabina EP, Ramya SR, Preety P, Patel S, Mandal N, Mishra PP and Samuel J (2010). Hepatoprotective and antioxidant effects of gallic acid in paracetamol-induced liver damage in mice. J. Pharm. Pharmacol., **62**:638–643. Doi: 10.1211/jpp.62.05.0012.

34. Subramaniam S, Khan HBH, Elumalai N and Lakshmi SYS (2015). Hepatoprotective effect of ethanolic extract of whole plant of *Andrographis paniculata* against CCl4-induced hepatotoxicity in rats. *Comp Clin Path*., **24**: 1245-1251. Doi: 10.1007/s00580-015-2067-2
35. Singh D, Arya PV, Sharma A, Dobhal MP and Gupta RS (2015). Modulatory potential of α-amyrin against hepatic oxidative stress through antioxidant status in Wistar albino rats. *J Ethnopharmacol.,* **161**:186-193. Doi: 10.1016/j.jep.2014.12.025.
36. Talib WH and Abukhader MM (2013). Combinatorial Effects of Thymoquinone on the Anticancer Activity and Hepatotoxicity of the Prodrug CB 1954. *Sci Pharm.,* **81**:519-30. Doi: 10.3797/scipharm.1211-15.
37. Shanmugam T and Selvaraj M (2013). Epigallocatechin gallate effectively ameliorates fluoride-induced oxidative stress and DNA damage in the liver of rats. *Canadian Journal of Physiology and Pharmacology*., **91**:528-537. Doi: 10.1139/cjpp-2012-0347.
38. Tuzcu M, Orhan C, Muz OE, Sahin N, Juturu V, and Sahin K (2017). Lutein and zeaxanthin isomers modulates lipid metabolism and the inflammatory state of retina in obesity-induced high-fat diet rodent model. *BMC ophthalmology.*, **17**:1. Doi: 10.1186/s12886-017-0524-1.
39. Vivoli E, Cappon A, Milani S, Piombanti B, Provenzano A, Novo E, Masi A, Navari N, Narducci R, Mannaioni G, Moneti G, Oliveira PC, Parola M, and Marra F (2016). NLRP3 inflammasome as a target of berberine in experimental murine liver injury: Interference with $P2X_7$ signalling. *Clin. Sci.,* **130**: 1793–1806. Doi: 10.1042/CS20160400.
40. Wu YL, Jiang YZ, Jin XJ, Lian LH, Piao JY, Wan Y, Jin HR, Joon LJ, and Nan JX (2010). Acanthoic acid, a diterpene in Acanthopanax koreanum, protects acetaminophen-induced hepatic toxicity in mice. Phytomedicine., **17**: 475–479. Doi: 10.1016/j.phymed.2009.07.011.
41. Yao You-Li, Han Xin, Li Zhi-Man, Lian Li-Hua, Nan Ji-Xing and Wu Yan-Ling (2017). Acanthoic Acid Can Partially Prevent Alcohol Exposure-Induced Liver Lipid Deposition and Inflammation. *Frontiers in Pharmacology*., **8**: 134. Doi: 10.3389/fphar.2017.00134
42. Yao HT, Yang YC, Chang CH, Yang HT, and Yin MC (2015). Protective effects of (-)-epigallocatechin-3-gallate against acetaminophen-induced liver injury in rats. Biomedicine., **5**: 15. Doi: 10.7603/s40681-015-0015-8
43. Yousef MI, Omar, SA, El-Guendi MI and Abdelmegid LA (2010). Potential protective effects of quercetin and curcumin on paracetamol-induced histological changes, oxidative stress, impaired liver and kidney functions and haematotoxicity in rat. Food Chem. Toxicol., **48**:3246–3261. Doi: 10.1016/j.fct.2010.08.034.
44. Zhang J, Song Q, Han X, Zhang Y, Zhang X, Chu X, Zhang F, and Chu L (2017). Multi-targeted protection of acetaminophen-induced hepatotoxicity in mice by tannic acid. Int. Immunopharmacol., **47**:95–105. Doi: 10.1016/j.intimp.2017.03.027.