# FLAVONOIDS AND THE LIVER—A REVIEW

**Mehmed Abtulov, Stefka Valcheva-Kuzmanova**

*Department of Pharmacology and Clinical Pharmacology and Therapeutics, Faculty of Medicine, Medical University of Varna, Bulgaria*

## ABSTRACT

**INTRODUCTION: Liver diseases (hepatitis, steatosis, non-alcoholic fatty liver disease, cirrhosis and hepatocellular carcinoma) are among the most common causes of disability and death worldwide. An accumulating body of evidence has established a relationship between the intake of polyphenol-rich foods and beverages and the lower incidence of liver diseases. Flavonoids are important ingredients in human diet.**

**AIM: The aim or the present review article was to summarize the current knowledge about the effects of flavonoids on liver health and the mechanisms involved.**

**MATERIALS AND METHODS: Literature in Pubmed, Google Scholar and ScienceDirect has been studied and analyzed.**

**RESULTS: Flavonoids protect the liver from viral, toxic, drug-induced and obesity-associated liver damage, but the data are almost exclusively derived from animal studies. However, the number of clinical trials is insufficient and additional human studies are needed to confirm their effect in clinical practice.**

**CONCLUSION: Analysis of the literature data from scientific databases showed promising hepatoprotective effects of flavonoids proved predominantly in experimental animal studies.**

**Keywords:** *flavonoids, hepatoprotective, liver, review*

## INTRODUCTION

Liver diseases (hepatitis, steatosis, non-alcoholic fatty liver disease—NAFLD, cirrhosis and hepatocellular carcinoma—HCC) are among the most common causes of disability and death worldwide. It is estimated that 2 million deaths per year are due to complications of these conditions (1). The etiology of liver diseases includes alcohol abuse, viral infections, medications, rising incidence of metabolic syndrome and autoimmunity (2–5). Inflammation, oxidative stress and abnormal immune response play central role in the pathogenesis of these diseases (6). These scientific data serve as valuable tools for seeking new therapeutic options, including phytotherapeutic ones.

Polyphenols (PPs) are natural compounds ubiquitously presented in fruits, vegetables, tea, coffee and other beverages. They contribute to the bitter or astringent taste of foods. PPs protect plants against aggressive factors such as ultraviolet radiation and infectious agents as well as attract pollinators (7). Generally, PPs are divided into two groups: flavonoids and non-flavonoids. The main flavonoids include flavones, flavonols, flavan-3-ols (flavanols), flavanones, isoflavones and anthocyanins (Fig.1). It is estimated that the mean daily flavonoid intake in

**Address for correspondence:**
*Mehmed Abtulov*
*Faculty of Medicine*
*Medical University of Varna*
*55 Marin Drinov St*
*9002 Varna*
*e-mail: Mehmed.Abtulov@mu-varna.bg*

**Received**: June 16, 2021
**Accepted**: June 27, 2021

European adults is as high as 428 ± 49 mg (8). In the last decade flavonoids have attracted scientific interest due to their numerous health benefits. An accumulating body of evidence has established a relationship between the intake of polyphenol-rich (including flavonoid-rich) foods and beverages and the lower incidence of liver diseases (9).

## AIM

The current contribution is focused on the effects of different classes of flavonoids on liver health and the mechanisms involved.

## MATERIALS AND METHODS

Databases such as PubMed, ScienceDirect and Google Scholar were used to collect and analyze the scientific data.

## RESULTS

### *Flavones*

The most studied flavones include apigenin, luteolin, and tangeretin. A number of pre-clinical studies have identified the role of these compounds in the prevention and treatment of liver diseases (10–17). Most of the experiments are conducted with the use of a hepatotoxic agent or with a specific experimental model associated with liver damage.

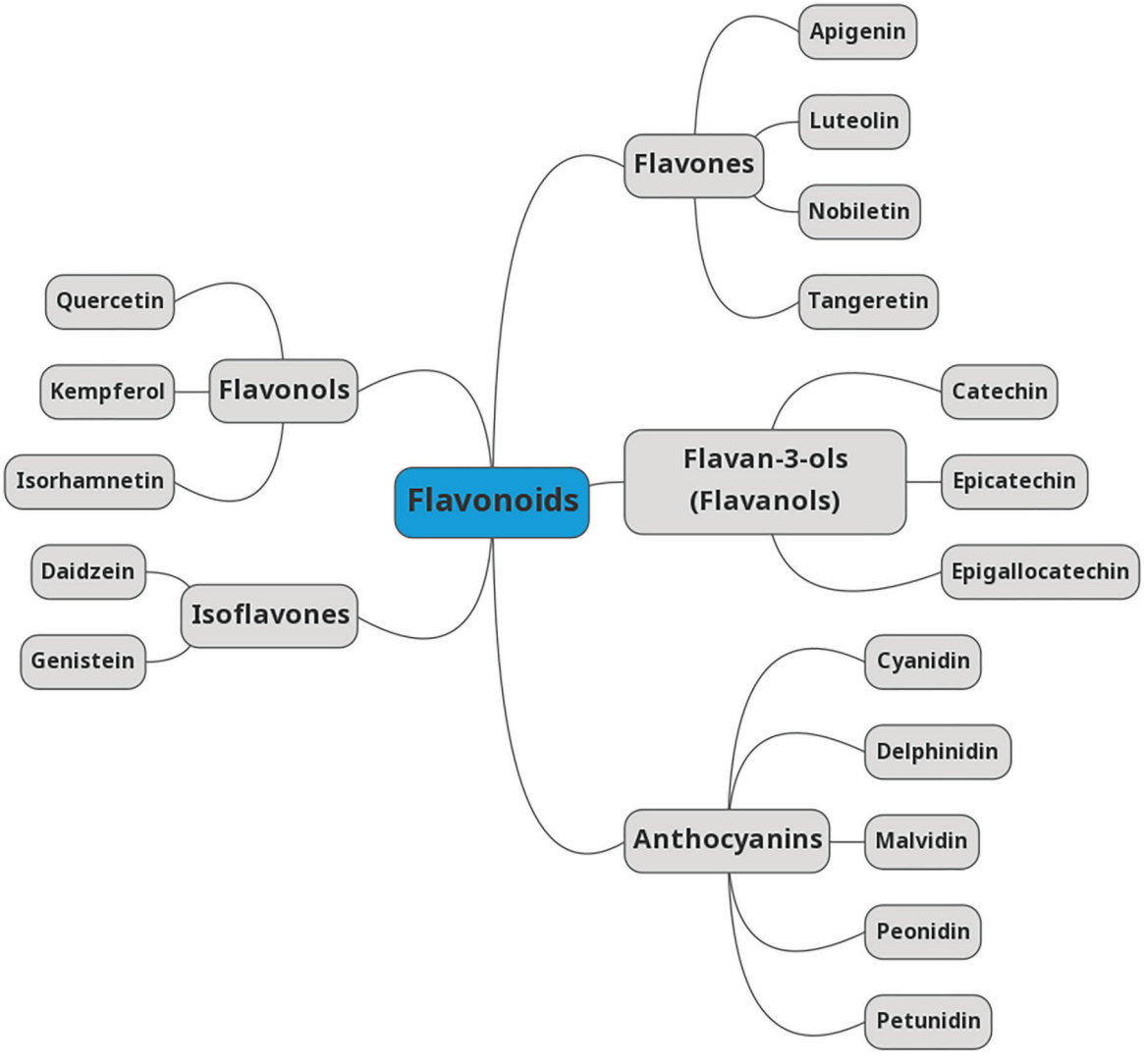


*Fig. 1. Flavonoids—classification*

The literature review shows that apigenin suppresses hepatic inflammation and oxidative damage, decreases the fibrotic tissue in the liver, alleviates liver steatosis, and prevents hepatocyte death. Moreover, it prevents liver damage by stimulating the cellular antioxidant defense system (free radical scavenging; activation of the antioxidant enzymes—superoxide dismutase, glutathione peroxidase, glutathione reductase, glutathione S-transferase) (10–12). It also suppresses of the pro-inflammatory pathways (non-canonical NF-κB pathway) (10), modulates sirtuin 1 activity (involved in oxidative stress and inflammatory response) (12), and alleviates hepatocyte autophagy and apoptosis (13,14). Nonetheless, one animal study revealed a dose-dependent hepatotoxic effect of apigenin through oxidative damage when injected intraperitoneally (15). Currently, there are no documented clinical trials with apigenin used as a phytotherapeutic agent. Further human studies are needed to clarify the effects of this flavone on the liver.

Luteolin is found in broccoli, pepper, thyme, and celery (16). Studies suggest that this flavone can suppress hepatic fibrosis through induction of apoptosis of the fibrotic tissue forming hepatic stellate cells and improve NAFLD by regulating lipid metabolism, suppressing the inflammation, and enhancing the antioxidant defense system of hepatocytes (18-22, 24). There are no clinical trials assessing the hepatic effects of luteolin.

In terms of liver effects, tangeretin has been mostly studied for its potential antitumor activity (against HCC). *In vitro* and in vivo studies have revealed that its potential anticancer effects are due to improved intercellular connections between hepatocytes, suppressed proliferation and migration of malignant cells, tumor cell cycle arrest and induction of apoptosis of the cancer cells (25–27). In another model, tangeretin counteracted the hepatotoxic effects of the chemotherapeutic agent cisplatin by suppressing the activity of pro-inflammatory cytokines, up-regulation of anti-inflammatory cytokines and stimulating the oxidative stress-combating enzymes (26).

### *Flavonols*

Quercetin is the most broadly investigated flavonol—a flavonoid with a ketone group. It is present in vegetables (onion, kale, tomato), fruits (apple, grapes, berries), and beverages (tea, red wine) (17).

Both in vivo and *in vitro* studies underline the role of quercetin in preventing liver damage caused by obesity (28,29), drugs (chemotherapeutic agents) (30) and toxins (alcohol) (31). Quercetin protects the liver by preventing VLDL processing and hepatic storage, ameliorating liver inflammation and oxidative stress as well as by stimulating ethanol-metabolizing enzyme systems (19–23).

Quercetin possesses pro-oxidant properties, which determine its anti-cancer activity. Intracellularly, this flavonol is converted to *o*-quinone, which exerts dose-dependent cytotoxic effects. However, local enzymes, such as nicotinamide adenine dinucleotide phosphate oxidase (NADPH oxidase) or NAD(P)H:quinone reductase (DT-diaphorase), restore the cellular level of quercetin, which could be a mechanism of preventing intact cell damage. Moreover, this flavonoid induces apoptosis and leads to death of malignant cells in HCC, as documented *in vitro* (32) and in vivo (33). Additionally, quercetin acts as a "sensitizer" to boost the efficacy of other chemotherapeutic approaches investigated for HCC therapy (33).

### *Flavan-3-ols (Flavanols)*

These chemical compounds are found in high quantities in green tea (*Camellia sinensis*), cocoa, and banana. The main flavanols include catechin, epicatechin, epigallocatechin, and epigallocatechin gallate (EGCG). The literature review highlights the role of these flavonoids (especially EGCG) in the prevention and treatment of NAFLD and HCC. According to the results from preclinical studies, flavan-3-ols exert beneficial effects in NAFLD due to their antioxidant, anti-inflammatory and energy metabolism-regulating activities. The intimate mechanisms of these protective effects include: weight loss, stimulation of LDL-cholesterol clearance and suppressed triglyceride synthesis, activation of hepatic adenosine monophosphate (AMP)-activated protein kinase (central regulator of the energy metabolism), improved mitochondrial respiration, enhanced insulin sensitivity and reduced expression of fibrosis-stimulating molecules in the liver (transforming growth factor-beta—TGF-β and collagen I-α1) (34). Although results from clinical trials confirmed

these benefits, the study samples are small, the administrated doses or used substances are different, which could explain some of the discrepancies observed. For instance, pure EGCG administration did not produce the same protective effect as mixed catechins in green tea extract (35).

The HCC preventive effects of green tea catechins are broadly studied and documented. A number of *in vitro* studies reported that they induced apoptosis of cancer cells and reduced the expression of growth factors (insulin-like growth factor 1/2, platelet-derived growth factor, epidermal growth factor) and their receptors (36). In vivo preclinical studies (animals with experimental models of liver cancer) confirmed these effects. Furthermore, most of them were described in metabolic syndrome models of liver carcinogenesis (36). Although clinical trials with green tea catechins found a relation between higher polyphenol intake and reduced risk of certain benign or malignant tumors (colorectal adenomas, colorectal carcinoma, prostate carcinoma, leucoplakia), the effects on the risk of HCC were conflicting and inconclusive. Indeed, a review reported no decrease in the incidence of HCC (37). The authors suggested the design of the studies presumably contributed to the observed results.

A potential drawback of catechins might be their ability to induce hepatotoxicity. Review of the published data shows that green tea catechins induce several xenobiotic-metabolizing cytochrome (CYP) isoforms (CYP1A2, CYP2D6, CYP2C9, and CYP3A4) and produce cytotoxic metabolites (acting as pro-oxidants). Interestingly, most of the reported cases of liver toxicity involve women (38). These data should be taken into account when conducting a clinical trial.

### *Flavanones*

Citrus fruits (orange, lemon, lime) are rich sources of flavanones (naringenin, hesperidin). It is estimated that flavanone content may vary between 180 and 740 mg/L according to the citrus species (39).

Naringenin has well-documented effects on the liver health. It has been shown to protect the liver from toxic (alcohol, carbon tetrachloride, heavy metals), pro-oxidant or viral damage as well as from malignant transformation (40). Alcohol is known to induce liver damage and fibrosis through oxidative stress, acetaldehyde accumulation, alternation in CYP2E1 activity and lipid accumulation. Naringenin prevents these damaging effects through induction of the alcohol-metabolizing enzyme alcohol dehydrogenase (thus decreasing acetaldehyde), suppression of free radical formation and scavenging. Carbon tetrachloride ($CCl_4$) is a hepatotoxic agent, used in experimental medicine to induce liver fibrosis and cirrhosis. Naringenin prevents $CCl_4$-induced fibrotic changes in the liver by suppressing its metabolism to toxic $CCl_3OO^{\cdot}$ radical, preventing the activity of apoptotic pathways, down-regulating the inflammatory cytokines (interleukin-1/6 and tumor necrosis factor-α) and enzymes (cyclooxygenase-2 and inducible nitric oxide synthase), preventing the activity of the pro-fibrotic factor TGF-β. As a strong antioxidant, it prevents oxidative stress-mediated liver changes (including from heavy metals) through stimulating the antioxidant defense system in the body (superoxide dismutase, glutathione, glutathione peroxidase, catalase). Furthermore, this flavanone is shown to possess antiviral properties through inhibiting non-structural proteins (such as NS2, NS5A) of the hepatitis C virus. The anticancer activity is thought to be due to its antioxidant effects, inhibition of signaling pathways (MAP kinase, PI3/AKT, NF-κB) activation of p53 (tumor suppressor gene), G0/G1 phase arrest, induction of apoptosis (due to cytochrome c release) and suppression of the angiogenesis (mediated by vascular endothelial growth factor) (41). Similar benefits (without antiviral activity) are documented for the other flavanone—hesperidin (41,42).

### *Isoflavones*

Genistein, daidzein, puerarin and formononetin belong to the group of isoflavone-type flavonoids. They are highly present in legumes (soybeans) and red clover (*Trifolium pratense*) (43). In rodent models of obesity and metabolic syndrome, high intake of these phenols was inversely associated with the development of liver disease (alcoholic, non-alcoholic) and its progression. In addition, knockout mice models of dyslipidemia were improved with high consumption of genistein and formononetin. Unexpectedly, the last was potent enough to induce liver steatosis in one of the studies although it alleviated liver inflammation in animals fed a cholesterol-rich diet. It is supposed that isoflavones inhibit aldose re-

ductase activity and polyol pathway (thus, the production of fructose in the liver), activate peroxisome proliferator-activated receptor-alpha (PPAR-α), alleviate CYP21E-mediated oxidative stress and endotoxin-mediated NF-κB activation (44).

The number of clinical studies with isoflavones is limited. One study among 6786 Chinese adults revealed that isoflavonoid intake is associated with lower risk of NAFLD, hyperlipidemia, and arterial hypertension (45).

Although isoflavones possess phytoestrogenic activity, they do not tend to increase the risk of estrogen-dependent malignant conditions (such as endometrial, breast and liver cancer) in females, when consumed in a dietary level (<100 mg/day) (46,47). Moreover, these compounds elicit anti-estrogenic activity. Therefore, some authors report improvement in hyperestrogenic states with isoflavone consumption (48).

### *Anthocyanins*

Anthocyanins (ACNs) (cyanidin, delphinidin, malvidin, peonidin, petunidin) are responsible for the blue to purple color of fruits, vegetables and flowers. The average daily intake ranges between 180 mg and 215 mg. Although they have low bioavailability, regular dietary intake has shown to possess positive impact on liver lipid metabolism and lowers the risk of NAFLD (49). *In vitro* studies on HepG2 hepatoma cells have revealed that both cyanidin and total ACN extract promote lipolysis and inhibit lipogenesis, thus reduce the lipid accumulation in the liver. Additionally, ACNs stimulate AMPK-pathway and PPAR-mediated lipid metabolism. In vivo studies with healthy, obese, metabolic syndrome or steatohepatitis rats/mice have identified similar outcomes. The available evidence supports the *in vitro* effects of ACNs with effect on the lipid storage in the liver. In those experiments, ACNs were associated with weight loss, improved insulin resistance and reduced severity of steatohepatitis.

Anthocyanins belong to the strongest antioxidants and protect the liver from oxidative damage. Such effects are documented in vivo in studies with sweet potato (50,51), bilberry (52) and chokeberry

*Table 1. In vitro and in vivo investigations of the effects of flavonoids on the liver*

| Described Effect | In Vitro Studies | Animal Studies | Human Studies |
|---|---|---|---|
| ***Anti-inflammatory*** | Yue et al.(10) | Yue et al. (10); Wang et al. (11); Zhang et al. (24); Omar et al. (26); Yang et al. (29); Chen et al. (31); Popović et al. (52) | Guo et al. (58) |
| ***Antioxidant*** | Zhai et al. (12); Kondeva-Burdina et al. (56) | Wang et al. (11); Zhai et al. (12); Wang et al. (23); Zhang et al. (24); Omar et al. (26); Yang et al. (29); Chen et al. (31); Choi et al. (50); Jiang et al. (51); Popović et al. (52); Valcheva-Kuzmanova et al. (53): Valcheva-Kuzmanova et al. (54); Valcheva-Kuzmanova et al. (55) | Guo et al. (58) |
| ***Antifibrotic*** | *Ji et al. (13); Li et al. (18)* | *Ji et al (13); Li et al. (18);* Popović et al. (52) | |
| ***Antihyperlipidemic*** | Zhu et al. (28); Yang et al. (29) | Kwon et al. (19); Liu et al. (20); Yin et al. (22); Omar et al. (26); Zhu et al. (28); Yang et al. (29) | Chang et al. (57) |
| ***Anti-apoptotic*** | Tsaroucha et al. (14) | Tsaroucha et al. (14); Omar et al. (26) | Guo et al. (58) |
| ***Anti-cancer*** | Zheng et al. (25); Chaumontet et al. (27); Zhou et al. (32); Zou et al. (33); Banjerdpongchai et al. (42) | | |
| ***Insulin-sensitizing*** | | | Zhang et al. (59) |

(52–56). For instance, *Aronia melanocarpa* (chokeberry) juice (rich in anthocyanins) administered both as pretreatment or post-treatment in a model of $CCL_4$-induced hepatotoxicity, has shown a very good hepatoprotective effect accompanied by antioxidant activity (53, 54). Moreover, the protective effect of *Aronia*-derived anthocyanins on liver lipid peroxidation was comparable to that of quercetin (55). The protective effect of anthocyanin-rich *Aronia melanocarpa* fruit juice has been also described in a model of tert-butyl hydroperoxide-induced hepatotoxicity and oxidative stress on isolated rat hepatocytes (56).

However, as with other flavonoids, there are few clinical studies conducted with ACNs. In one of them, *H. sabdariffa* extract improved liver steatosis after 3 months (57). Another study showed that anthocyanin-rich bayberry (myrica) juice improved the oxidative stress, inflammation and apoptosis in individuals with NAFLD (58). Zhang et al. assessed the liver benefits of purified bilberry and black currant ACN extracts and found that they improve insulin resistance, markers of hepatic injury and the clinical evolution of NAFLD (59).

Table 1 sums up the *in vitro* and in vivo studies investigating the effects of flavonoids on liver health:

In summary, many studies have been concentrated on the investigation of the effects of flavonoids on the liver. Based on the available scientific data flavonoids possess multiple mechanisms responsible for their documented hepatoprotective effects such as exerting anti-inflammatory, antioxidant, antiapoptotic, antihyperlipidemic, anticancer, antiviral, and antifibrotic effect. However, still the number of clinical studies is limited, therefore, more and more precise clinical studies are needed to explore their effects in real patients with liver diseases.

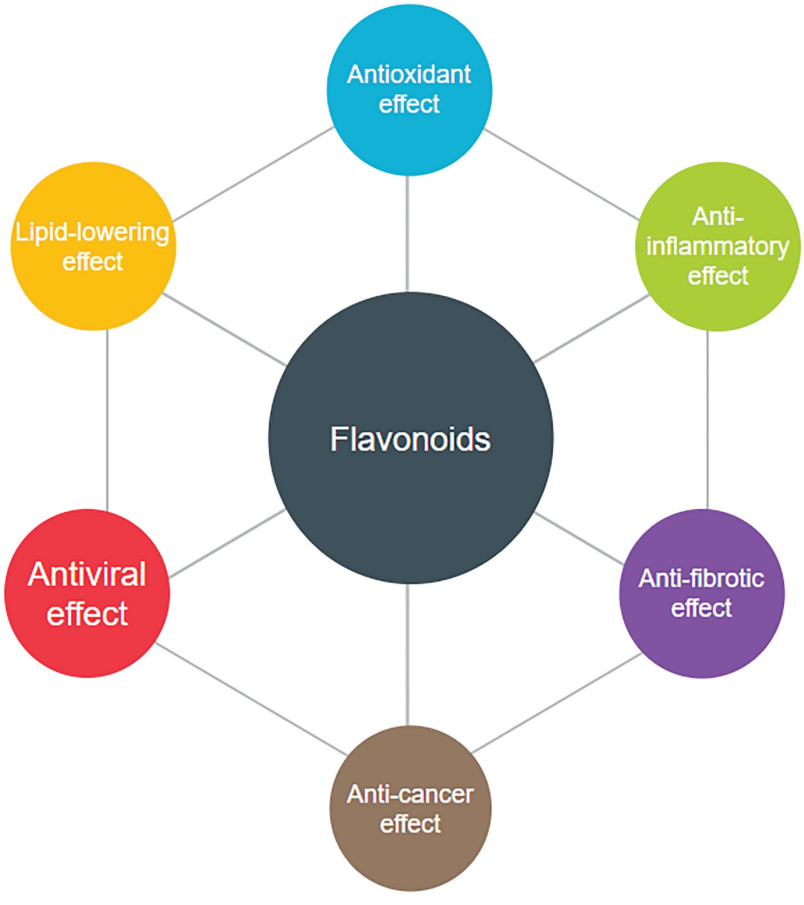


*Fig. 2. Mechanisms of hepatoprotective effects of flavonoids*

Fig. 2 summarizes the mechanisms involved in the hepatoprotective effects of the flavonoids.

## CONCLUSION

Flavonoids are important ingredients in human diet. Analysis of the literature data from scientific databases shows promising hepatoprotective effects of flavonoids in experimental settings. However, the number of clinical trials is insufficient and additional human studies are needed to confirm their effect in clinical practice.

## REFERENCES


1. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151-71. doi: 10.1016/j.jhep.2018.09.014.
2. Ohashi K, Pimienta M, Seki E. Alcoholic liver disease: A current molecular and clinical perspective. Liver Res. 2018;2(4):161-72. doi: 10.1016/j.livres.2018.11.002.
3. Katarey D, Verma S. Drug-induced liver injury. Clin Med (Lond). 2016 ;16(Suppl 6):s104-9. doi: 10.7861/clinmedicine.16-6-s104.
4. Kim D, Touros A, Kim WR. Nonalcoholic fatty liver disease and metabolic syndrome. Clin Liver Dis. 2018;22(1):133-40. doi: 10.1016/j.cld.2017.08.010.
5. Carbone M, Neuberger JM. Autoimmune liver disease, autoimmunity and liver transplantation. J Hepatol. 2014;60(1):210-23. doi: 10.1016/j.jhep.2013.09.020.
6. Li S, Hong M, Tan HY, Wang N, Feng Y. Insights into the role and interdependence of oxidative stress and inflammation in liver diseases. Oxid Med Cell Longev. 2016;2016:4234061. doi: 10.1155/2016/4234061.
7. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009;2(5):270-8. doi: 10.4161/oxim.2.5.9498.
8. Vogiatzoglou A, Mulligan AA, Lentjes MA, Luben RN, Spencer JP, Schroeter H, et al. Flavonoid intake in European adults (18 to 64 years). PLoS One. 2015;10(5):e0128132. doi: 10.1371/journal.pone.0128132.
9. Rasouli H, Farzaei MH, Khodarahmi R. Polyphenols and their benefits: A review. Int J Food Prop. 2017;20(Suppl 2):1700-41. doi:10.1080/10942912.2017.1354017.
10. Yue S, Xue N, Li H, Huang B, Chen Z, Wang X. Hepatoprotective effect of apigenin against liver injury via the non-canonical NF-κB pathway in vivo and in vitro. Inflammation. 2020;43(5):1634-48. doi: 10.1007/s10753-020-01238-5.
11. Wang F, Liu JC, Zhou RJ, Zhao X, Liu M, Ye H, et al. Apigenin protects against alcohol-induced liver injury in mice by regulating hepatic CYP2E1-mediated oxidative stress and PPARα-mediated lipogenic gene expression. Chem Biol Interact. 2017;275:171-7. doi: 10.1016/j.cbi.2017.08.006.
12. Zhao L, Zhang J, Hu C, Wang T, Lu J, Wu C, et al. Apigenin prevents acetaminophen-induced liver injury by activating the SIRT1 pathway. Front Pharmacol. 2020;11:514. doi: 10.3389/fphar.2020.00514.
13. Ji J, Yu Q, Dai W, Wu L, Feng J, Zheng Y, et al. Apigenin alleviates liver fibrosis by inhibiting hepatic stellate cell activation and autophagy via TGF-β1/Smad3 and p38/PPARα pathways. PPAR Res. 2021;2021:6651839. doi: 10.1155/2021/6651839.
14. Tsaroucha AK, Tsiaousidou A, Ouzounidis N, Tsalkidou E, Lambropoulou M, Giakoustidis D, et al. Intraperitoneal administration of apigenin in liver ischemia/reperfusion injury protective effects. Saudi J Gastroenterol. 2016;22(6):415-22. doi: 10.4103/1319-3767.195556.
15. Singh P, Mishra SK, Noel S, Sharma S, Rath SK. Acute exposure of apigenin induces hepatotoxicity in Swiss mice. PLoS One. 2012;7(2):e31964. doi: 10.1371/journal.pone.0031964.
16. Nabavi SF, Braidy N, Gortzi O, Sobarzo-Sanchez E, Daglia M, Skalicka-Woźniak K, et al. Luteolin as an anti-inflammatory and neuroprotective agent: A brief review. Brain Res Bull. 2015;119(Pt A):1-11. doi: 10.1016/j.brainresbull.2015.09.002.
17. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016;5:e47. doi: 10.1017/jns.2016.41.
18. Li J, Li X, Xu W, Wang S, Hu Z, Zhang Q, et al. Antifibrotic effects of luteolin on hepatic stellate cells and liver fibrosis by targeting AKT/mTOR/p70S6K and TGFβ/Smad signalling pathways. Liver Int. 2015;35(4):1222-33. doi: 10.1111/liv.12638.
19. Kwon EY, Jung UJ, Park T, Yun JW, Choi MS. Luteolin attenuates hepatic steatosis and insulin resistance through the interplay between the liver and adipose tissue in mice with diet-induced obesity. Diabetes. 2015;64(5):1658-69. doi: 10.2337/db14-0631.

**20.** Liu G, Zhang Y, Liu C, Xu D, Zhang R, Cheng Y, et al. Luteolin alleviates alcoholic liver disease induced by chronic and binge ethanol feeding in mice. J Nutr. 2014;144(7):1009-15. doi: 10.3945/jn.114.193128.

**21.** Domitrović R, Jakovac H, Grebić D, Milin C, Radosević-Stasić B. Dose- and time-dependent effects of luteolin on liver metallothioneins and metals in carbon tetrachloride-induced hepatotoxicity in mice. Biol Trace Elem Res. 2008;126(1-3):176-85. doi: 10.1007/s12011-008-8181-0.

**22.** Yin Y, Gao L, Lin H, Wu Y, Han X, Zhu Y, et al. Luteolin improves non-alcoholic fatty liver disease in db/db mice by inhibition of liver X receptor activation to down-regulate expression of sterol regulatory element binding protein 1c. Biochem Biophys Res Commun 2017;482:720-6. doi: 10.1016/j.bbrc.2016.11.101.

**23.** Wang Z, Liu Y, Zhao X, Liu S, Liu Y, Wang D. Aronia melanocarpa prevents alcohol-induced chronic liver injury via regulation of Nrf2 signaling in C57BL/6 Mice. Oxid Med Cell Longev. 2020;2020:4054520. doi: 10.1155/2020/4054520.

**24.** Zhang H, Tan X, Yang D, Lu J, Liu B, Baiyun R, et al. Dietary luteolin attenuates chronic liver injury induced by mercuric chloride via the Nrf2/NF-κB/P53 signaling pathway in rats. Oncotarget. 2017;8(25):40982-93. doi: 10.18632/oncotarget.17334.

**25.** Zheng J, Shao Y, Jiang Y, Chen F, Liu S, Yu N, et al. Tangeretin inhibits hepatocellular carcinoma proliferation and migration by promoting autophagy-related BECLIN1. Cancer Manag Res. 2019;11:5231-42. doi: 10.2147/CMAR.S200974.

**26.** Omar HA, Mohamed WR, Arab HH, Arafa el-SA. Tangeretin alleviates cisplatin-induced acute hepatic injury in rats: targeting MAPKs and apoptosis. PLoS One. 2016;11(3):e0151649. doi: 10.1371/journal.pone.0151649.

**27.** Chaumontet C, Bex V, Gaillard-Sanchez I, Seillan-Heberden C, Suschetet M, Martel P. Apigenin and tangeretin enhance gap junctional intercellular communication in rat liver epithelial cells. Carcinogenesis. 1994;15(10):2325-30. doi: 10.1093/carcin/15.10.2325.

**28.** Zhu X, Xiong T, Liu P, Guo X, Xiao L, Zhou F, et al. Quercetin ameliorates HFD-induced NAFLD by promoting hepatic VLDL assembly and lipophagy via the IRE1a/XBP1s pathway. Food Chem Toxicol. 2018;114:52-60. doi: 10.1016/j.fct.2018.02.019.

**29.** Yang H, Yang T, Heng C, Zhou Y, Jiang Z, Qian X, et al. Quercetin improves nonalcoholic fatty liver by ameliorating inflammation, oxidative stress, and lipid metabolism in db/db mice. Phytother Res. 2019;33(12):3140-52. doi: 10.1002/ptr.6486.

**30.** Sánchez-González PD, López-Hernández FJ, Dueñas M, Prieto M, Sánchez-López E, Thomale J, et al. Differential effect of quercetin on cisplatin-induced toxicity in kidney and tumor tissues. Food Chem Toxicol. 2017;107(Pt A):226-36. doi: 10.1016/j.fct.2017.06.047.

**31.** Chen X. Protective effects of quercetin on liver injury induced by ethanol. Pharmacogn Mag. 2010;6(22):135-41. doi: 10.4103/0973-1296.62900.

**32.** Zhou J, Fang L, Liao J, Li L, Yao W, Xiong Z, et al. Investigation of the anti-cancer effect of quercetin on HepG2 cells in vivo. PLoS One. 2017;12(3):e0172838. doi: 10.1371/journal.pone.0172838.

**33.** Zou H, Zheng YF, Ge W, Wang SB, Mou XZ. Synergistic anti-tumour effects of quercetin and oncolytic adenovirus expressing TRAIL in human hepatocellular carcinoma. Sci Rep. 2018;8(1):2182. doi: 10.1038/s41598-018-20213-7.

**34.** Chen C, Liu Q, Liu L, Hu YY, Feng Q. Potential biological effects of (-)-epigallocatechin-3-gallate on the treatment of nonalcoholic fatty liver disease. Mol Nutr Food Res. 2018;62(1):1700483. doi: 10.1002/mnfr.201700483.

**35.** Masterjohn C, Bruno RS. Therapeutic potential of green tea in nonalcoholic fatty liver disease. Nutr Rev. 2012;70(1):41-56. doi: 10.1111/j.1753-4887.2011.00440.x.

**36.** Shimizu M, Shirakami Y, Sakai H, Kubota M, Kochi T, Ideta T, et al. Chemopreventive potential of green tea catechins in hepatocellular carcinoma. Int J Mol Sci. 2015;16(3):6124-39. doi: 10.3390/ijms16036124.

**37.** Jin X, Zheng RH, Li YM. Green tea consumption and liver disease: a systematic review. Liver Int. 2008;28(7):990-6. doi: 10.1111/j.1478-3231.2008.01776.x.

**38.** Mazzanti G, Menniti-Ippolito F, Moro PA, Cassetti F, Raschetti R, Santuccio C, et al. Hepatotoxicity from green tea: a review of the literature and two unpublished cases. Eur J Clin Pharmacol. 2009;65(4):331-41. doi: 10.1007/s00228-008-0610-7.

**39.** Barreca D, Gattuso G, Bellocco E, Calderaro A, Trombetta D, Smeriglio A, et al. Flavanones: cit-

rus phytochemical with health-promoting properties. Biofactors. 2017;43(4):495-506. doi: 10.1002/biof.1363.

**40.** Hernández-Aquino E, Muriel P. Beneficial effects of naringenin in liver diseases: molecular mechanisms. World J Gastroenterol. 2018;24(16):1679-707. doi: 10.3748/wjg.v24.i16.1679.

**41.** Tabeshpour J, Hosseinzadeh H, Hashemzaei M, Karimi G. A review of the hepatoprotective effects of hesperidin, a flavanon glycoside in citrus fruits, against natural and chemical toxicities. Daru. 2020;28(1):305-17. doi: 10.1007/s40199-020-00344-x.

**42.** Banjerdpongchai R, Wudtiwai B, Khaw-On P, Rachakhom W, Duangnil N, Kongtawelert P. Hesperidin from citrus seed induces human hepatocellular carcinoma HepG2 cell apoptosis via both mitochondrial and death receptor pathways. Tumour Biol. 2016;37(1):227-37. doi: 10.1007/s13277-015-3774-7.

**43.** Křížová L, Dadáková K, Kašparovská J, Kašparovský T. Isoflavones. Molecules. 2019;24(6):1076. doi: 10.3390/molecules24061076.

**44.** Qiu LX, Chen T. Novel insights into the mechanisms whereby isoflavones protect against fatty liver disease. World J Gastroenterol. 2015;21(4):1099-107. doi: 10.3748/wjg.v21.i4.1099.

**45.** Wang X, Wang Y, Xu W, Lan L, Li Y, Wang L, et al. Dietary isoflavones intake is inversely associated with non-alcoholic fatty liver disease, hyperlipidaemia and hypertension. Int J Food Sci Nutr. 2021:1-11. doi: 10.1080/09637486.2021.1910630.

**46.** Messina MJ, Wood CE. Soy isoflavones, estrogen therapy, and breast cancer risk: analysis and commentary. Nutr J. 2008;7:17. doi: 10.1186/1475-2891-7-17.

**47.** Colacurci N, De Franciscis P, Atlante M, Mancino P, Monti M, Volpini G, et al. Endometrial, breast and liver safety of soy isoflavones plus Lactobacillus sporogenes in post-menopausal women. Gynecol Endocrinol. 2013;29(3):209-12. doi: 10.3109/09513590.2012.738724.

**48.** Carbonel AAF, Simões RS, Girão JHC, Sasso GRDS, Bertoncini CRA, Sorpreso ICE, et al. Isoflavones in gynecology. Rev Assoc Med Bras (1992). 2018;64(6):560-4. doi: 10.1590/1806-9282.64.06.560.

**49.** Valenti L, Riso P, Mazzocchi A, Porrini M, Fargion S, Agostoni C. Dietary anthocyanins as nutritional therapy for nonalcoholic fatty liver disease. Oxid Med Cell Longev. 2013;2013:145421. doi: 10.1155/2013/145421.

**50.** Choi JH, Choi CY, Lee KJ, Hwang YP, Chung YC, Jeong HG. Hepatoprotective effects of an anthocyanin fraction from purple-fleshed sweet potato against acetaminophen-induced liver damage in mice. J Med Food. 2009;12(2):320-6. doi: 10.1089/jmf.2007.0691.

**51.** Jiang Z, Chen C, Wang J, Xie W, Wang M, Li X, et al. Purple potato (Solanum tuberosum L.) anthocyanins attenuate alcohol-induced hepatic injury by enhancing antioxidant defense. J Nat Med. 2016;70(1):45-53. doi: 10.1007/s11418-015-0935-3.

**52.** Popović D, Kocić G, Katić V, Zarubica A, Veličković LJ, Ničković VP, et al. Anthocyanins protect hepatocytes against $CCl_4$-induced acute liver injury in rats by inhibiting pro-inflammatory mediators, polyamine catabolism, lipocalin-2, and excessive proliferation of Kupffer cells. Antioxidants (Basel). 2019;8(10):451. doi: 10.3390/antiox8100451.

**53.** Valcheva-Kuzmanova S, Borisova P, Galunska B, Krasnaliev I, Belcheva A. Hepatoprotective effect of the natural fruit juice from Aronia melanocarpa on carbon tetrachloride-induced acute liver damage in rats. Exp Toxicol Pathol. 2004;56(3):195-201. doi: 10.1016/j.etp.2004.04.012.

**54.** Valcheva-Kuzmanova SV, Popova PB, Galunska BT, Belcheva A. Protective effect of Aronia melanocarpa fruit juice pretreatment in a model of carbon tetrachloride-induced hepatotoxicity in rats. Folia Med (Plovdiv). 2006;48(2):57-62.

**55.** Valcheva-Kuzmanova S. Comparative study of the protective effect of Aronia melanocarpa fruit juice and quercetin in a model of paracetamol-induced hepatotoxicity in rats. J Biomed Clin Res. 2015;8(2):118-23. doi:10.1515/jbcr-2015-0161

**56.** Kondeva-Burdina M, Valcheva-Kuzmanova S, Markova T, Mitcheva M, Belcheva A. Effects of Aronia melanocarpa Fruit Juice on Isolated Rat Hepatocytes. Pharmacogn Mag. 2015;11(Suppl 4):S592-7. doi: 10.4103/0973-1296.172967.

**57.** Chang HC, Peng CH, Yeh DM, Kao ES, Wang CJ. Hibiscus sabdariffa extract inhibits obesity and fat accumulation, and improves liver steatosis in humans. Food Funct. 2014;5(4):734-9. doi: 10.1039/c3fo60495k.

**58.** Guo H, Zhong R, Liu Y, Jiang X, Tang X, Li Z, et al. Effects of bayberry juice on inflammatory

and apoptotic markers in young adults with features of non-alcoholic fatty liver disease. Nutrition. 2014;30(2):198-203. doi: 10.1016/j.nut.2013.07.023.

**59.** Zhang PW, Chen FX, Li D, Ling WH, Guo HH. A CONSORT-compliant, randomized, double-blind, placebo-controlled pilot trial of purified anthocyanin in patients with nonalcoholic fatty liver disease. Medicine (Baltimore). 2015;94(20):e758. doi: 10.1097/MD.0000000000000758.