
FLAVONOIDS AND THE LIVER—A REVIEW

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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 of 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 in-

fections, 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

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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.

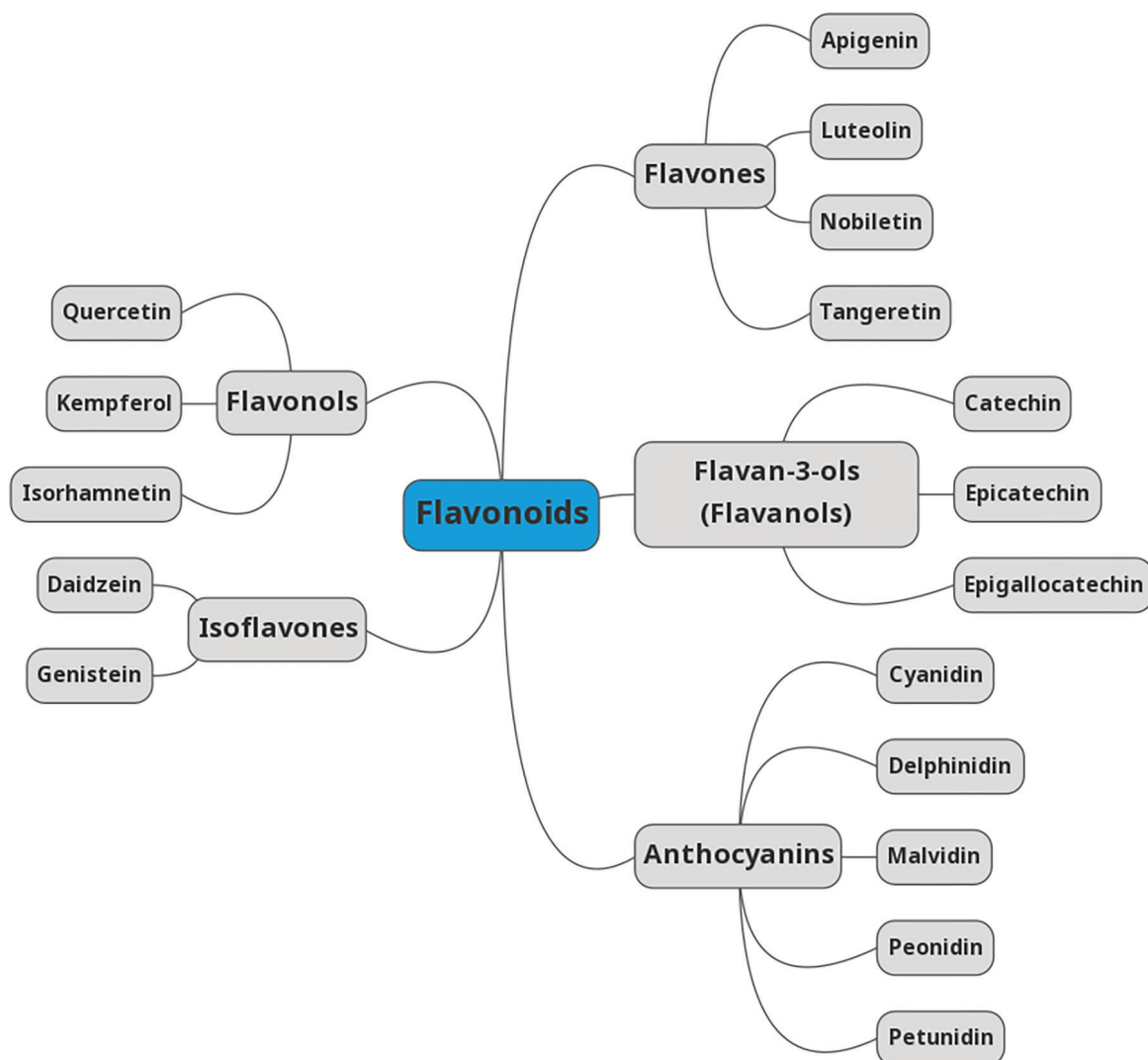


Fig. 1. Flavonoids—classification

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- κ B 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 pres-

ent 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- α 1) (34). Although results from clinical trials confirmed

these benefits, the study samples are small, the administered 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 oxida-

tive 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 (CCl₄) is a hepatotoxic agent, used in experimental medicine to induce liver fibrosis and cirrhosis. Naringenin prevents CCl₄-induced fibrotic changes in the liver by suppressing its metabolism to toxic CCl₃OO 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- κ B) 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- α (PPAR- α), alleviate CYP21E-mediated oxidative stress and endotoxin-mediated NF- κ B 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 CCL₄-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.

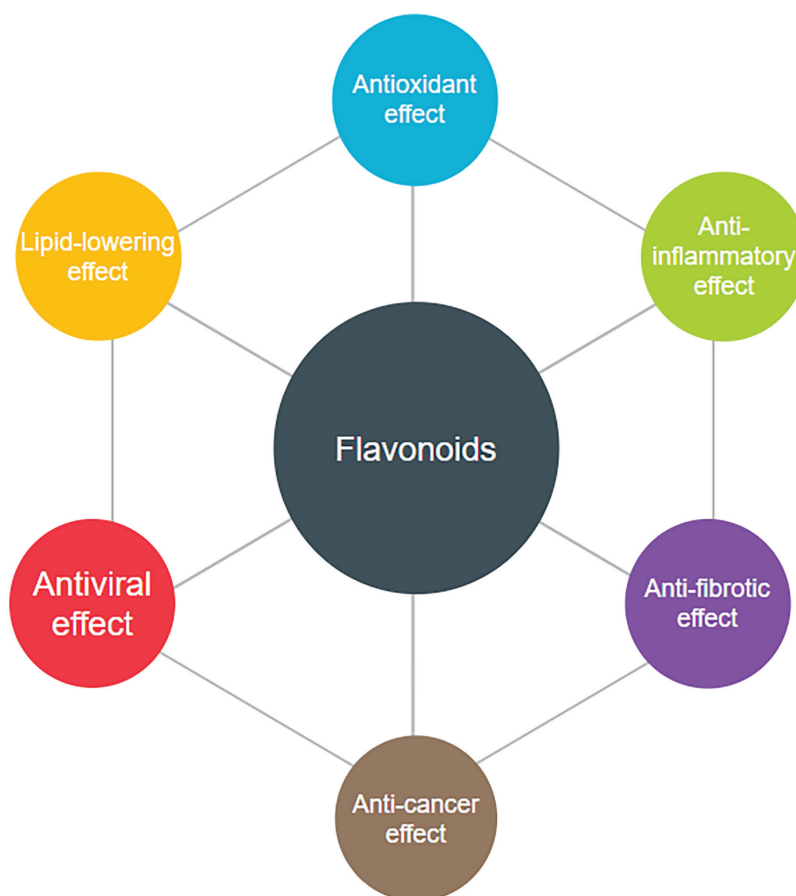


Fig. 2. Mechanisms of hepatoprotective effects of flavonoids

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.

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