УДК 615.322:547.972.35:616.36(048.8) Scientific reviews

THE ROLE OF QUERCETIN IN THE TREATMENT OF LIVER DISEASES: THE REVIEW BASED ON EXPERIMENTAL AND CLINICAL INVESTIGATIONS

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Key words: *quercetin, non-alcoholic fatty liver disease, hepatitis, liver fibrosis.*

Bukovinian Medical Herald. 2022. V. 26, № 3 (103). P. 97-102.

DOI: *10.24061/2413-0737.XXVI.3.103.2022.16*

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Abstract. *Scientific review covers current data regarding the role of quercetin in the therapeutic corrections of various liver diseases, in particular non-alcoholic fatty liver disease, chronic hepatitis, drug-induced liver disease.*

The aim of the review *was to sum up current scientific data regarding quercetin properties, its mechanism of action and possibilities of this flavonoid in the treatment of various liver diseases.*

Conclusions. *Quercetin is found to possess antioxidant, anti-inflammatory, hypolipidemic, antisteatotic and antifibrotic properties. The abovementioned makes this flavonoid potentially useful in the treatment of various liver disease, in particular non-alcoholic fatty liver disease, chronic hepatitis of different etiologies, and drug induced liver disease.*

РОЛЬ КВЕРЦЕТИНУ У ЛІКУВАННІ ЗАХВОРЮВАНЬ ПЕЧІНКИ: ОГЛЯД ЕКСПЕРИМЕНТАЛЬНИХ ТА КЛІНІЧНИХ ДОСЛІДЖЕНЬ

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Ключові слова: *кверцетин, неалкогольна жирова хвороба печінки, гепатит, фіброз печінки.*

Буковинський медичний вісник. 2022. Т. 26, № 3 (103). С. 97-102.

Резюме. *Науковий огляд присвячений узагальненню сучасних даних щодо ролі кверцетину в терапевтичній корекції різних захворювань печінки, з-поміж яких: неалкогольна жирова хвороба печінки, хронічний гепатит, медикаментозно-асоційовані захворювання печінки.*

Мета дослідження *– узагальнити сучасні наукові дані щодо властивостей кверцетину, механізму його дії та можливостей застосування цього флавоноїду в лікуванні різних захворювань печінки.*

Висновки. *Встановлено, що кверцетин має антиоксидантні, протизапальні, гіполіпідемічні, антистеатотичні та антифібротичні властивості. Вищезазначене свідчить про потенційну користь цього флавоноїду у терапії різних захворювань печінки, зокрема неалкогольної жирової хвороби печінки, хронічних гепатитів різної етіології та медикаментозно-асоційованих захворювань печінки.*

Introduction. Quercetin belongs to the group of flavanols – compounds of plant origin containing the main structural elements in the form of two aromatic rings A and B, connected by a three-carbon bridge, which forms pyran or pyrone (in the presence of double bond) cycle. These compounds possess antiradical activity against superoxide, hydroxyl radicals and lipid peroxide radical, acting as donors of electrons or hydrogen atoms. Quercetin increases activity of catalase and tocopherol, reduces thiobarbituric acid reactive substances content [1, 26, 30]. Flavonoids can be presented in the form of glycosides (with attached carbohydrate molecules – glycosyl groups) and aglycones (without attached carbohydrate molecules) [4, 26]. Flavonoids are characterized by a high antioxidant activity, which is most pronounced in quercetin, stimulate protein synthesis, regulate phospholipid metabolism, and possess membrane-stabilizing properties [14].

The aim of the review was to sum up current scientific data regarding quercetin properties, its mechanism of action and possibilities of this flavonoid in the treatment of various liver diseases.

Discussion. The effect of quercetin on metabolism of carbohydrates, cholesterol, and triacylglycerols is being actively studied [24, 50]. Oral administration of quercetin in animals with metabolic syndrome improves insulin sensitivity and tolerance to carbohydrates, decreases visceral fat tissue and oxidative stress level, increases endogenous synthesis of nitrogen monoxide, and improves blood rheological properties [2]. Quercetin prevents accumulation of visceral and liver fat, an increase of cholesterol, triacylglycerols, glucose, and pro-inflammatory adipokines in the blood in the experiment on mice kept on a high-calorie diet for twenty weeks [27]. Results indicating dose-dependent features of its properties on lipid and carbohydrate metabolism are obtained in clinical studies. In particular, in the study carried out by S. Egert et al., quercetin in daily dose of 150 mg/day is found to reduce atherogenic low density lipoproteins (LDL)

plasma concentration in overweight and obese patients with metabolic syndrome [16]. However, administration of 50 mg/day of this compound does not produce a significant effect on the content of lipids and lipoproteins in the blood [17].

Quercetin reduces lipoxygenase activity, which plays a key role in the processes of atherogenesis. The active metabolite of quercetin, quercetin-3-glucuronide, inhibits the endothelium-dependent oxidation of LDL in the endothelial cells of blood vessels, thus revealing its anti-atherosclerotic effect [25]. In humans quercetin inhibits platelet aggregation and thrombus formation [23] by reducing thromboxane B2 synthesis in particular [26]. Quercetin contributes to the improvement of coronary blood circulation by inhibiting thrombogenesis and biosynthesis of vasoconstrictors and increasing elasticity of the coronary arteries. In case of acute cardiac ischemia, it reduces hemodynamic disturbances and the area of the necrotic myocardium due to inhibition of phospholipids breakdown and decrease in the concentration of free fatty acids in the cardiomyocyte membranes, as well as reduction of lipoxygenase activity [3]. Quercetin has anti-inflammatory properties due to inhibition of 5-lipooxygenase, which contributes to decline in leukotrienes synthesis from arachidonic acid. Furthermore, this flavonoid also reduces protein kinase C and calmodulin-dependent protein kinase activity [26].

The antitumor effect of this flavonoid is associated with tumor cell growth factors inhibition, decrease in the intensity of protein phosphorylation in tumor cells, decline of the protein kinase C activity, and probably potentiation of the chemotherapeutic agent action [22]. Flavonoids, and quercetin in particular, are known to reduce the risk of cancer of the colon [28], kidney [47], and pancreas [13].

Quercetin possesses valuable pharmacological properties for the treatment of various liver diseases: non-alcoholic fatty liver disease (NAFLD), chronic hepatitis, drug induced liver diseases and liver fibrosis etc. This flavonoid can influence on the development and advance of liver diseases via different pathways providing antioxidant, anti-inflammatory and antisteatotic effects together with inhibition of cellular apoptosis [41]. Furthermore, quercetin is found to have different mechanisms of action at different stages of pathological process in the liver, including regulation of peroxisome proliferation activator receptor (PPAR), uncoupling proteins and perilipin 2-related factors via brown fat activation in liver steatosis. Meanwhile, this compound inhibits stromal extracellular matrix deposition at the stage of liver fibrosis, affecting transforming growth factor-β1 (TGF-β1), endoplasmic reticulum stress, and apoptosis [55].

The use of quercetin reduces activity of cytolytic and cholestatic syndromes in patients with liver diseases [11, 12]. Quercetin provides normalization of the liver functional activity, regression of peroxidation syndromes and systemic inflammation in type 2 diabetes mellitus patients with hepatosis [5]. The water-soluble form of quercetin used in the experimental studies was found to help in reduction of cholesterol, triacylglycerols, glucose, total bilirubin levels, alanineaminotransferase (ALT) and alkaline phosphatase (AP) activities, and to decline prooxidant / antioxidant system disorders in the liver [6]. The experimental study of HepG2 cells, in which steatosis was modified and then treated with quercetin, showed a decrease in the triacylglycerols content, insulin resistance, pro-inflammatory cytokines synthesis and increase in the antioxidants concentration, indicating that quercetin can be effective in the treatment of NAFLD [45]. H.Z. Ying et al. in the experiment of alimentary modeling of steatohepatitis in gerbils found that administration of quercetin in the dose of 30 and 60 mg/kg per day reduced triacylglycerols content and the size of lipid droplets in the liver, serum transaminases activity and pro-inflammatory mediators such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). Collagen levels in the liver decreased in animals treated with quercetin in the dose of 60 mg/kg [50]. M. Kobori et al. investigated that the normalizing effect of quercetin on lipid metabolism was mediated through the regulation of expression of the corresponding genes. In particular, high-calorie diet-induced increase of PPAR-γ gene expression, sterol regulatory element-binding protein-1c (SREB-1c) and first apoptosis signal genes in mice, which promote lipid accumulation, were normalized after quercetin administration. At the same time, increased proliferation of PPAR-α receptors, the transcription factor that regulates fatty acid oxidation, was observed, and its proliferation is reduced under conditions of a high-fat diet (HFD) [27].

Another study has shown that quercetin and repaired feed reduce expression of SREBP-1c mRNA in the liver elevated as a result of HFD. Quercetin in the dose of 50 mg/kg and 100 mg/kg improved liver cells' pathological profile in HFD-associated NAFLD as well. Thus, the authors have shown that quercetin possesses an inhibitory effect on SREBP-1c expression and improves liver pathology in NAFLD mice [39].

In experimental studies on mice H. Yang et al. revealed that quercetin alleviated serum transaminase levels and markedly reduced type 2 diabetes mellitus-induced histological alterations of the liver of NAFLD mice. Additionally, quercetin restored superoxide dismutase, catalase, and glutathione content in the liver. Moreover, quercetin markedly attenuated type 2 diabetes mellitus-induced production of interleukin-1β (IL-1β), IL-6, and TNF-α [49]. M. Gori et al. by means of a novel organs-on-chip technology investigated that quercetin seemed to restrain the progression of free fatty acid-induced hepatocellular steatosis, showing a cytoprotective effect due to its antioxidant and lipid-lowering properties [20]. Y. Zhang et al. revealed a positive effect of isorhamnetin, quercetin metabolite, in reducing excess weight and liver steatosis severity [53].

There could be several pathways demonstrating how quercetin acts in case of NAFLD. Quercetin ameliorates HFD-induced NAFLD by promoting hepatic very low density lipoproteins assembly and lipophagy by inositol-requiring enzyme 1α / X-box binding protein spliced signaling pathway [56]. A positive role of quercetin in HFD could be realized via down-regulation of nuclear factor-κB (NF-κB), the transcriptional factor that stimulates inflammation, and the up-regulation of heme

oxygenase-1 (HO-1), carnitine palmitoyltransferase 1 and nuclear factor erythroid 2-related factor 2 (NRF-2), one of the major defense systems against stress-related injury [35]. Quercetin intake correlates with an increased expression of carnitine palmitoyltransferase-1a, a regulator of fatty acid oxidation in the liver and the heart [35]. P. Liu et al. have found, that quercetin improves hepatic steatosis by enhancing frataxin-mediated phosphatase and tensin homolog-induced pyruvate kinase 1 / Parkin-dependent mitophagy, which can serve as a potential preventive mechanism for NAFLD progression [31].

Quercetin is able to reduce levels of cytochrome P450 family 2 E member 1 (CYP2E1), and thus reduces CYP2E1 mediated oxidative stress. Quercetin is found to decrease obesity-induced hepatosteatosis by increasing mitochondrial oxidative metabolism via HO-1, stimulating hepatic mitochondrial oxidative metabolism [42]. Finally, quercetin is found to increase adiponectin level, an adipokine with insulin-sensitizing and antisteatotic actions [10, 33].

Another possible pathway of favorable influence of quercetin in case of NAFLD is its regulatory effect on gut microbiota that could be altered in this case. D. Poras et al. have found that quercetin supplementation decreases insulin resistance and NAFLD activity score, by reducing intrahepatic lipid accumulation via its ability to modulate lipid metabolism gene expression, CYP2E1-dependent lipoperoxidation and related lipotoxicity. Quercetin reverts gut microbiota imbalance and related endotoxemia-mediated toll like receptor-4 (TLR-4) pathway induction, with subsequent inhibition of inflammasome response and reticulum stress pathway activation, leading to the blockage of lipid metabolism gene expression deregulation. The authors support the suitability of quercetin as a therapeutic approach for obesity-associated NAFLD via its anti-inflammatory, antioxidant and prebiotic integrative properties [36].

Clinical investigations revealed that additional quercetin prescription to the basic treatment of NAFLD patients in the dose of 40 mg three times daily caused more effective improvement of cytolysis and metabolic intoxication [8, 37]. In addition, γ-glutamyltransferase (GGT) activity is reduced more effectively in patients with additional quercetin intake that reflects alleviation of the endogenous intoxication. Positive effect of quercetin on lipid profile in NAFLD patients was noted as well, and lowering of the total cholesterol and triacylglycerols concentration in the blood was found [8, 37], that confirms its hypolipidemic and antiatherogenic properties [16, 25]. Decrease of TNF-α plasma level with quercetin treatment was investigated. Similar results concerning reduction of TNF-α plasma concentration under the influence of quercetin administration were found in the experimental studies performed by H.Z. Ying et al. [50]. Meanwhile, the content of interleukin-10 (IL-10) in the blood did not significantly change during the treatment. Significant decline of the proatrial natriuretic peptide (proANP) concentration in the blood after the treatment with quercetin was found [9]. The abovementioned indicates its positive cardiotropic properties, as it is established that proANP is an accurate marker of cardiovascular insufficiency [19, 43, 51], which is also noted by other scientists [3, 21].

Except its favorable influence in case of NAFLD, quercetin was investigated in experimental and clinical studies of the treatment of chronic hepatitis of different etiologies. Quercetin ameliorated liver damage and histopathological changes, and suppressed the release of inflammatory cytokines in the experimental model of autoimmune hepatitis. This flavonoid attenuated apoptosis and autophagy in concanavalin-induced autoimmune hepatitis by inhibiting TNF-associated receptor factor 6 / c-Jun N-terminal kinase pathway [48].

S. Lee et al. investigated that quercetin and its glucoside derivatives prevented ethanol-induced hepatotoxicity by decreasing hepatic aminotransferase activities and inflammatory response in HepG2 cells. Moreover, quercetin induced detoxifying enzymes via the nuclear accumulation of the NRF2 and induction of antioxidant response element gene [29]. Quercetin could elevate the expression of NRF2 / HO-1 and ameliorate ethanol-induced acute liver injury in rats. The underlying mechanism of quercetin's benefit on the liver combines its antioxidant properties and inhibitory effect on the reactive oxygen species / nuclear factor-κB / nucleotide-binding oligomerization-like receptor family pyrin domain containing 3 inflammasome / IL-1β and interleukin-18 pathway via inducing HO-1. Besides, quercetin upregulated the anti-inflammatory cytokine IL-10, while it was found uncorrelated with HO-1 expression [32].

Histopathological analyses revealed that treatment with quercetin markedly decreased collagen deposition, pseudolobuli development, and hepatic stellate cells activation. NF-κB and TGF-β synthesis decreased after treatment with quercetin, indicating that antifibrotic effect of quercetin is associated with its ability to modulate NF-κB and TGF-β production. These results suggest that quercetin may be an effective therapeutic strategy in the treatment of patients with liver damage and fibrosis [46]. In addition to quercetin, dihydroquercetin has been investigated concerning its hepatoprotective effects in the treatment of toxic hepatitis and liver fibrosis by enhancing antioxidant enzyme activity and decreasing the pro-oxidant effect [15].

According to H. Farghali et al., quercetin alleviated D-galactosamine / lipopolyssacharide-induced acute hepatotoxicity by silent information regulator T1 (SIRT1) upregulation [18]. Also, experimental research showed that 50 mg/kg of quercetin can alleviate acrylamide-induced hepatotoxicity by reducing oxidative stress and inflammatory injury and regulating lipid metabolism [52]. Quercetin was less effective in cadmium induced hepatotoxicity as it was shown in the experiments carried out by C. Vicente-Sánchez et al. whose results demonstrated that cadmium administration induced an increased marker enzyme of liver injury activity in plasma. This effect was not inhibited by quercetin. However, the administration of quercetin alleviated cadmium-induced oxidative damage [44].

Quercetin co-administration prevented the elevation of ALT, aspartate transaminase (AST), AP and bilirubin compared with isoniazid and rifampicin treatment alone in

experiment. The authors observed that quercetin prophylaxis lessened the severity of hepatic necrosis and inflammation in the histological analysis, as compared to those who received only anti-tuberculosis drugs. Quercetin attenuated anti-tuberculosis drug-induced oxidative stress by increasing NRF2 activation and expression, enhancing endogenous antioxidant levels. Quercetin blocked inflammatory mediators of high mobility group box-1 (HMGB-1) and interferon-γ (IFN-γ), inhibiting activation of NF-κB / TLR-4 axis [40]. Similar results of a beneficial effect of quercetin in isoniazid hepatotoxicity were obtained by Y. Zhang et al., who investigated quercetin pretreatment reduced ALT and AST levels, improved liver histopathological changes and substantially mitigated apoptosis in rats [54].

In clinical studies chronic nonviral hepatitis patients who took quercetin were characterized by more effective reduce of ALT and AST activities as compared to patients who received standard treatment [7, 38]. These results are consistent with L.M. Sheremeta data, who have found out similar properties of quercetin in the experimental modeling of hepatitis [11]. Furthermore, lactate dehydrogenase and AP activities decreased in quercetin arm as well. GGT activity was more effectively decreased in patients who received a comprehensive treatment with quercetin [7, 38]. These findings reflect intoxication and cholestatic syndromes reduction in the examined patients. Administration of quercetin revealed a positive effect on lipid profile. In particular, decrease in the total cholesterol concentration in the blood was found [9].

Patients with additional quercetin intake were characterized by a significant decrease in TNF-α content in the blood, while patients receiving standard treatment demonstrated only a tendency to reduction of this proinflammatory cytokine. No reliable changes in anti-inflammatory IL-10 level in chronic hepatitis patients of both quercetin and standard treatment arms were detected [9, 38]. According to C. Montoliu et al. investigations, proANP is not only a reliable predictor of cardiovascular risk in cardiological patients but also can serve as a marker for the risk of hemodynamic complications in patients with chronic liver disease [34]. In this respect, additional to the standard treatment quercetin prescription caused significant decrease of proANP level, lessening concomitant cardio-vascular alterations in chronic hepatitis patients.

Conclusions. Quercetin is found to possess antioxidant, anti-inflammatory, hypolipidemic, antisteatotic and antifibrotic properties. The abovementioned makes this flavonoid potentially useful in the treatment of various liver disease, in particular non-alcoholic fatty liver disease, chronic hepatitis of different etiologies, and drug induced liver disease.

Prospects for further investigations. More investigations are required to specify dose-related effects of quercetin in various liver pathologies together with determination of duration of its intake and possible age-depended differences in dose and therapeutic scheme.

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Надійшла до редакції 28.08.22

Рецензент – проф. Ванчуляк О.Л.