Beneficial effects of rutin, quercitrin and quercetin on inflammatory bowel disease

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Received 24 March 2009 /Accepted 8 April 2009

SUMMARY

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The aim of this review article was to obtain a deeper understanding of the reported effects of flavonols, in particular rutin, quercitrin and their aglycone quercetin, with respect to their potential beneficial action on inflammatory bowel disease. Research in the field of flavonoids has increased significantly in recent few years and many new investigations have been performed concerning their absorption, metabolism, and probable mechanisms of action. Recently published results obtained in *in vitro* approaches and *in vivo* experiments on animal models are reported. Further investigation aimed at the clinical effects of rutin may be important for the development of a new therapeutic agent for the treatment of inflammatory bowel disease in humans.

Key words: inflammatory bowel disease – flavonols – absorption – metabolism – effects

Čes. a slov. Farm., 2009; 58, 47–54

SOUHRN

Příznivé účinky rutinu, kvercitrinu a kvercetinu na nespecifické střevní záněty

Cílem přehledného článku bylo dosáhnout hlubšího pochopení ve vědeckých časopisech publikovaných účinků flavonolů, zejména rutinu, kvercitrinu a jejich aglykonu kvercetinu, s důrazem na jejich potenciální příznivé působení u nespecifických střevních zánětů. Výzkum v oblasti flavonoidů v několika posledních létech významně vzrostl a objevila se řada nových skutečností týkajících se jejich absorpce, metabolismu a možných mechanismů účinků. Článek uvádí nedávno publikované výsledky získané v pokusech *in vitro* a experimentech *in vivo* na zvířecích modelech. Další výzkum zaměřený na klinické účinky rutinu může být důležitý pro vývoj nové léčivé látky k terapii nespecifických střevních zánětů v humánní medicíně.

Klíčová slova: nespecifické střevní záněty – flavonoly – absorpce – metabolismus – účinky

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Inflammatory bowel disease (IBD) refers to two major clinical conditions, i.e. ulcerative colitis (UC) and Crohn's disease (CD). UC is a refractory, chronic recurrent and non-specific inflammatory disease of rectal and colonic mucosa. Clinical manifestations include diarrhea, blood in the stool, abdominal pain, weight loss

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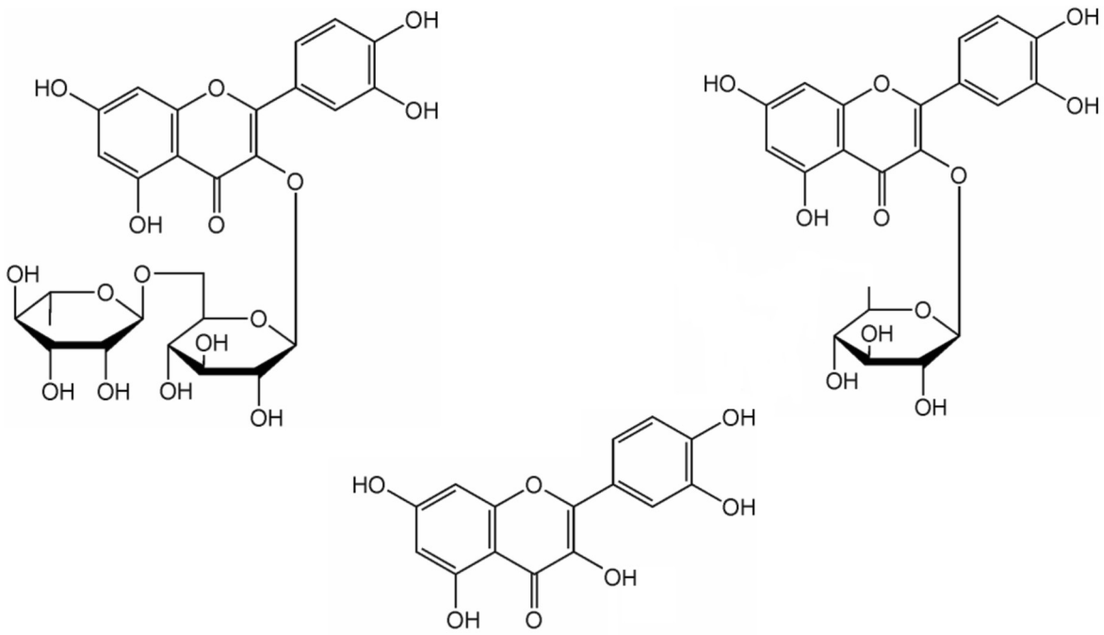

Fig. 1. Rutin (left), quercitrin (right) and their aglycone quercetin (middle)

and mucosal ulceration. CD can involve any part of gastrointestinal tract, but most frequently it involves the distal small intestine and colon. Patients with IBD often receive intense doses, i.e. the dosage schedule with multiple tablets several times a day, and long-term therapy that frequently requires lifelong treatment. The therapy is often accompanied with side effects associated with high dose intake resulting in low patient compliance which has a negative effect on the treatment.

As in other inflammatory processes, IBD is characterized by an up-regulation of the synthesis and release of a variety of pro-inflammatory mediators, such as eicosanoids, platelet activating factor, reactive oxygen and nitrogen metabolites and cytokines, thus influencing mucosal integrity and leading to excessive injury [1]. The cell types involved in the mucosal inflammatory response are similar to those found at systemic inflammatory sites including macrophages [2]. These cells have critical functions in the immune system, acting as regulators of homeostasis and as effector cells in infection, wound healing and tumor growth. However, macrophages do not always play a positive role in the homeostasis of the immune system. Under some circumstances, such as septic shock [3], rheumatoid arthritis [4], atherosclerosis and IBD [5], macrophages have been described to have noxious effects, probably due to the non-regulated and excessive secretion of inflammatory modulators such as reactive metabolites from oxygen or nitrogen and pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α), being deleterious to intestinal function. In fact, macrophages are considered to be the main source of these pro-inflammatory mediators in IBD, thus actively contributing to the pathology of these intestinal conditions [2, 6, 7].

Considering this, flavonoids are potential anti-inflammatory drugs applicable to IBD because firstly, these compounds are inhibitors of several enzymes which are activated in inflammation [7], secondly, a number of cells of the immune system are down-regulated by certain flavonoids *in vitro* [8], and thirdly, most flavonoids show potent antioxidative/radical scavenging effects [9, 10].

Flavonoids structure

Based on their molecular structure, flavonoids are divided into several groups, e.g. flavonols, flavones, flavanones, flavanols, and anthocyanins. All of them are phenylbenzopyrones with a basic structure formed by two benzene rings united through a heterocyclic pyrane or pyrone. Flavonols (i.e. rutin, quercitrin and quercetin) are characterized by the presence of a double bound in the central ring.

Among flavonoids, quercetin is the most common flavonoid in nature, and it is mainly present as its glycosylated forms such as quercitrin (3-rhamnosylquercetin) or rutin (rutoside, 3-rhamnosyl--glucosyl quercetin) [11] (Figure 1). *In vitro* studies have clearly shown that quercetin acts as a potent pleiotropic modulator in several physiological functions, showing different activities, such as an anti-proliferative effect in numerous cell lines [12, 13], a pro-apoptotic effect in lung carcinoma cell lines [14], and an inhibitory effect of osteoclastic differentiation [15]. It is important to note that when the glycosylated forms of quercetin are assayed, there is usually a loss of activity in these effects in comparison with those obtained with the aglycone, due to the presence of the sugar moiety in the flavonoid structure [16]. On the contrary, both glycosides quercitrin and rutin have been shown to exert intestinal anti-inflammatory effects in experimental models of rat colitis [7, 17]. Both flavonoids have been reported to be

helpful on acute and chronic experimental colitis in the rat, acting via a mechanism ascribed to mucosal protection or enhancement of mucosal repair, in which protection against oxidative insult and/ or amelioration of colonic fluid absorption may play a role [6, 16, 18].

Absorption, Metabolism and Elimination

Understanding the absorption and metabolism of flavonoids is fundamental in determining their biological activity. In general, naturally occurring flavonoids are attached to sugar residues which affect the mechanism of absorption by altering their physicochemical properties and thus their ability to enter cells, or to interact with transporters and cellular (lipo)proteins [19, 20].

It is thought that ingested flavonoid glycosides are not easily absorbed in the gastrointestine due to their hydrophilicity; consequently, a large fraction of them reaches the large intestine where they could be metabolized by microbial glycosidases to liberate their aglycones and affect the (patho)physiology of the large intestine [20]. A different situation has been observed for aglycones. The rapid absorption of quercetin indicates that it probably takes place in the proximal part of the small intestine [21].

Although quercetin glycosides are subject to deglycosylation by enterobacteria for the absorption at large intestine, small intestine acts as an effective absorption site for glucose-bound glycosides (quercetin glucosides). This is because small intestinal cells possess a glucoside-hydrolyzing activity and their glucose transport system is capable of participating in the glucoside absorption [22]. Thus the first step metabolic change of orally administered flavonoid glucosides seems to be deglycosylation occurring in the small intestinal lumen [23, 24] as the non-enzymatic deglycosylation of flavonoids such as gastric hydrolysis was not found [25]. Epithelial cells of the gastrointestinal tract are the only cells of the body in contact with flavonoid glycosides; the other cells are reached only by flavonoid metabolites and degradation products [26]. Flavonoid glucosides undergo either luminal deglycosylation catalyzed by membrane bound enzymes [26] or enter the enterocytes in the form of glucosides requiring active transport [27] followed by intracellular hydrolysis. The transport across the intestinal enterocytes depends on the quality of the flavonoid aglycone moiety and the nature and position of the attached sugar. The mechanism of absorption of quercetin-4'-glucoside was shown to involve both interaction with the sodium-dependent glucose transporter (SGLT1) and luminal hydrolysis by lactase phlorizin hydrolase (LPH), whereas quercetin-3--glucoside was absorbed only following deglycosylation by LPH [19].

After passage into enterocytes, flavonoid glucosides are susceptible to hydrolysis by intracellular β-glucosidases, such as broad-specificity cytosolic β-glucosidase [28]. After absorption, aglycones are conjugated to glucuronide, sulphate, and/or methyl groups in the intestinal mucosa and inner tissues [29]. Uridin-diphosphate-glucuronyl transferases are membrane-bound enzymes, situated in the endoplasmic reticulum, expressed primarily in the liver but also present in the intestinal epithelium [30]. Quercetin glucuronides can be resecreted from apical surfaces of epithelial cells back to the intestinal lumen [31]. Quercetin-3-glucuronides were shown to be further metabolized: either by a methylation of the catechol moiety resulting in 3'-methylquercetin- and 4'-methylquercetin-glucuronides or by the deglucuronidation with subsequent sulfation in 3'-position [32].

Recently, it has been reported that LPH, located in the brush border of mammalian small intestine, could perform hydrolysis not only for flavonoid glucosides but also for some flavonoid glycosides [33]. Furthermore, it was observed that absorption of both quercetin and rutin from the small intestine of rat occurred. Rutin appeared to be absorbed much more slowly than quercetin. Both flavonoids were bound to the small intestinal tissue. This binding to the intestinal wall components may significantly limit their absorption from this site [34].

The colon is heavily colonized by microorganisms with a strong catalytic and hydrolytic potential against compounds of exogenous and endogenous origin [35]. Flavonoids neither absorbed in the stomach nor in the small intestine are propelled to the colon. Reaching the colon, they are subjected to deglycosylation and deconjugation by colonic bacteria, and are cleaved giving rise to ring fission products [22, 36]. Prior to absorption, rutin and quercetin must undergo deglycosylation, what cannot be fully achieved by the small intestinal enzymatic system but is possible by colon microflora. Rutin is transformed to its aglycone by the bacteria producing α-rhamnosidase and β-glucosidase [24] (Figure 2).

The type of ring fission depends on the type of flavonoids. Flavonols are degraded to phenylacetic acids and phenylpropionic acids which are finally oxidized (beta-oxidation) to benzoic acids [37]. These low molecular microbial metabolites of flavonoids exhibit several important biological activities, e.g. anti-platelet activity and cytotoxicity for tumor cell lines [38]. The arising cleavage products are absorbed from the colon or further metabolized. 3,4-dihydroxyphenylpropionic acid is degraded in the colon to phenylpropionic, 3-hydroxypropionic, and 4-hydroxypropionic acid, which are further metabolized by the liver giving rise to hippuric, 3-hydroxyhippuric, and 4-hydroxyhippuric acids [39].

Compounds absorbed from the intestines enter the liver via the portal vein; they are removed from the blood by the liver parenchymal cells and biotransformed [40]. Conjugation of the polar hydroxyl groups with glucuronic acid, sulfuric acid, glycine, or possibly glutathione [41] results in water-soluble conjugates. These conjugates are eliminated either from the liver with bile into the duodenum, or renally with the urine (Figure 2). The minimum molecular weight is one of the factors determining whether a compound or a conjugate will undergo billiary excretion. The molecular weight limit depends on particular species; it was reported to be around 500–600 Da in humans [42]. Human small intestinal microsomes were shown to hydrolyze quercetin glucuronides *in vitro*, but this activity was related to

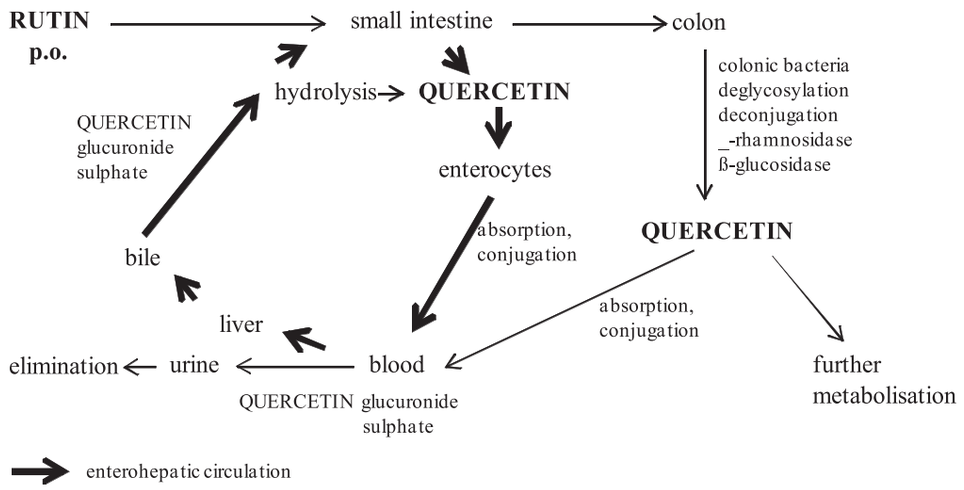

Fig. 2. Proposed pharmacokinetics of orally administered rutin

microsomal *ß*-glucuronidase. Thus deglucuronidation can occur when the flavonoid conjugate reaches the same cellular compartment [43]. So far no transport of glucuronides has been shown across the cell wall which would make them accessible for intracellular *ß*-glucuronidases. Deglucuronidation has not been reported in the gastrointestinal lumen yet due to other than microbial activity. However, deglucuronidation can occur during inflammation. *ß*-glucuronidase released from stimulated neutrophils or certain injured cells can hydrolyze flavonoid glucuronide to free aglycone possessing anti-inflammatory activities as reported for luteolin monoglucuronide [44]. High microbial *ß*-glucuronidase activity in the rat cecum content has also been observed [45]. Deconjugation of flavonoid metabolites coming from biliary clearance is thus possible to occur also in humans. In addition, flavonoid glucuronide and sulfate metabolites secreted with bile or in any other way into the small intestine could be hydrolyzed and the liberated aglycones would then pass into enterocytes passively, reabsorbed again, and metabolized forming thus an enterohepatic cycling [46, 47] (Figure 2).

In the plasma, flavonoids are present in conjugated forms as responsible reactions facilitate their excretion [29]. Systemic occurrence of quercetin in the conjugated form only was confirmed [48], free aglycone or parent glycosides were not detected. Quercetin metabolites have a lower but still significant inhibitory effect on lipid peroxidation and other biological activities as compared to the aglycone and these properties depend on the conjugation pattern [49]. Due to aromatic nucleus and hydroxyl substituents, flavonoids have a great affinity for proteins, particularly for albumin. The binding of quercetin to human albumin was found 70–80%. The presence of the unsaturated bound in the heterocyclic ring of flavonoids is crucial for this effect. Albumin-bound quercetin conjugates retained the antioxidative property.

The distribution of quercetin metabolites in tissues was investigated: high amount of them was observed in the digestive tract, low amount in the blood, liver, kidney, and lungs. The major metabolites in the intestine were quercetin-3-glucuronide, quercetin glucuronide sulphate, methyl-quercetin glucuronide (probably from biliary clearance) and quercetin [50].

Several papers report elimination of flavonoid metabolites by the urinary pathway. Quercetin is excreted in the urine in the form of glucuronide or sulphate [51].

As presented above, flavonoids undergo extensive metabolism after administration resulting in their altered structure. They were found in systemic circulation in the form of (methylated)glucuronide and/ or sulphate conjugates, whereby the hydroxyl groups are not available. Therefore, most of the effects shown in *in vitro* experiments with aglycones cannot be directly extrapolated to *in vivo* systems apart from the digestive tract where the possibility of direct interactions is obvious. This also concerns the antioxidant properties of flavonoids, which can be reduced. Even after being metabolized they may act locally or indirectly influence redox balance by inducing antioxidative enzymes, detoxifying enzymes, or compounds which may be involved in sustaining homeostasis [24].

Possible mechanisms of action – present status

The fundamental property of flavonoids, responsible for many of their beneficial effects, is their antioxidant capacity, allowing them to chelate ions of transition metals such as Fe^{2+}, Cu^{2+} or Zn^{2+}, to catalyze the electron transport, to scavenger reactive oxygen species (ROS) like the superoxide anion, oxygen singlet and lipidic peroxyradicals, or to stabilize free ROS by means of the hydrogenation or formation of complexes with oxidating species [52]. The antioxidant capacity of flavonoids presents a therapeutic potential in diseases, such as cardiovascular diseases [53], gastric or duodenal ulcers [54], cancer [55] or hepatic disorders [56]. Their antiviral and antiallergic actions are also important, as well as their anti-thrombotic and anti-inflammatory properties [52].

Flavonoids effects on a variety of inflammatory

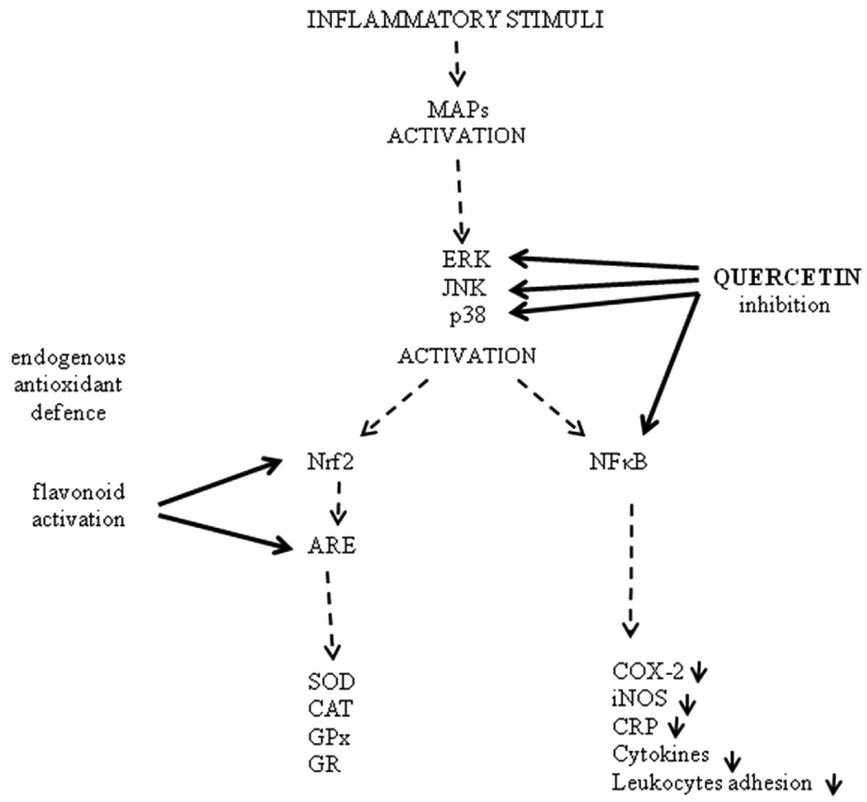

Fig. 3. Some effects of quercetin on the inflammatory cascade (adapted from [60])
In inflammation, three kinds of mitogen-activated proteins (MAPs), i.e. extracellular signal related kinase (ERK), Jun N-terminal kinase (JNK,) and p38 kinase are activated. Quercetin (right) was reported to inhibit iNOS expression through inhibition of p38 kinase and JNK, and to suppress pro-inflammatory cytokines and NFκB activation through ERK and p38 kinase. Flavonoids (left) are also reported to increase the endogenous antioxidant defense potential. The NF-E2 related factor 2 (Nrf2) is a redox sensitive factor whose nuclear translocation and binding to the antioxidant response elements (ARE) may result in the induction of antioxidant enzymes, i.e. superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR).

processes have been an object of diverse recent reviews and experimental studies, and it has been demonstrated that they are able to inhibit a series of enzymes activated during inflammatory process [57]. Prostaglandins and nitric oxide biosynthesis is involved in inflammation, and isoforms of inducible nitric oxide synthase (iNOS) and of cyclooxygenase (COX-2) are responsible for the production of a great amount of these mediators. *In vitro* studies have confirmed that quercetin inhibits nitric oxide production and the expression of iNOS. Some of these studies showed that quercetin down-regulates COX-2 expression in macrophages [58], human lymphocytes (*in vivo*) [59], and hepatic cells [60].

There are several steps at which flavonoids can modulate the cascade of molecular events leading to the over expression of iNOS or COX-2. They include inhibition of protein kinase C, phospholipases and phosphodiesterases [61], indirect modulation of iNOS by inhibition of the cyclooxygenase and/or lipooxygenase pathways, and some others [62]. Pathways inducing iNOS and COX-2 seem to converge in the activation of a transcription essential for the expression of pro-inflammatory genes, the nuclear factor kappa B (NFκB) [63]. The NFκB is one of the main factors whose modulation triggers a cascade of molecular events, some of which can constitute potential key targets for the treatment of inflammation. Inflammatory stimuli activate some cells, such as macrophages, which release cytokines (i.e. tumor necrosis factor alfa, TNFκ) and ROS.

In macrophages and other cell types, three kinds of mitogen-activated proteins (MAPs) are activated: extracellular signal related kinase (ERK), Jun N-terminal kinase (JNK), and p38 kinase [60] (Figure 3). Activated NFκB can stimulate the expression of iNOS with an increase in the nitric oxide formation. Its reaction with ROS produces the formation of peroxynitrite which contributes to cellular injury. Quercetin has been reported to inhibit iNOS expression through inhibition of p38 kinase [64] and JNK [65]. Quercetin is also able to suppress pro-inflammatory cytokines and NFκB activation through ERK and p38 kinase [66]. An elevation of reactive C protein (CRP) in serum is considered as the indicator of chronic inflammation. It is known that pro-inflammatory cytokine IL-6 induces CRP through NFκB activation [67]. Recent data demonstrate that flavonoids including quercetin reduce CRP level in some cells [68]. It is therefore probable that these effects on CRP expression could be mediated, at least partly, by the modulation of NFκB dependent pathway [60].

A variety of antioxidant defense systems as protection

from ROS have been developed in organisms. The major endogenous antioxidant systems include superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR). SOD catalyzes the dismutation of the superoxide radical anion, CAT and GPx convert H_2O_2 to H_2O, and GR recycles oxidized glutathione back to reduced form. The NF-E2 related factor 2 (Nrf2) is a redox-sensitive factor whose nuclear translocation and binding to the antioxidant response elements (ARE) may result in induction of antioxidant enzymes [69] (Figure 3). It has been reported that some flavonoids are Nrf2-ARE activators [70]. An increase in the endogenous antioxidant defense potential is thus additional mechanism which could contribute to the anti-inflammatory properties of flavonoids.

The immobilization and firm adhesion of leukocytes to the endothelial wall is another major mechanism responsible for the formation of oxygen-derived free radicals, but also for the release of cytotoxic oxidants and inflammatory mediators and further activation of the complement system. Under normal conditions, leukocytes move freely along the endothelial wall. However, during ischemia and inflammation, various mainly endothelium-derived mediators and complement factors may cause adhesion of the leukocytes to the endothelial wall resulting in the injury to tissues [23]. NFκB activation is a necessary step in the adhesion molecules [71]. Activated endothelial cells release IL-6 stimulating CRP production [72] contributing thus to the exacerbation of endothelial dysfunction. Infiltration of leukocytes into the mucosa significantly contributes to tissue necrosis and dysfunction. Neutrophils play crucial roles in the development of gastrointestinal inflammation. Neutrophils are recruited into the tissue by local production of IL-8, which is the primary chemotactic factor of neutrophils, and can then contribute to tissue destruction. In gastrointestinal inflammation, bacterial pathogens or cytokines induce the production of IL-8 by intestinal epithelial cells, and this may be followed by the migration of neutrophils. Some evidence suggests that IL-8 is significantly up-regulated in primary intestinal epithelial cell cultures from patients with IBD [73].

Beneficial effects on IBD

Beneficial effects of rutin and quercitrin (in some studies also quercetin) on IBD have been reported in many papers. In some of them, rutin and quercitrin act as quercetin deliverers to the large intestine [20].

Rutin, quercitrin, quercetin, and their metabolites can ameliorate conditions in the inflamed intestine through several mechanisms. The most investigated and reported one is their anti-oxidative effect. It can be helpful in scavenging of free radicals by means of interfering with several enzymes such as nitric oxide synthase, thereby resulting in decreased oxidative tissue injury. In addition, the suppression of pro-inflammatory cytokines, i.e. IL-1ß, IL-6 [57], IL-8 [73] and the key mediator for the expression of inflammatory cytokines TNF-α has been demonstrated [74, 75]. This can improve regulation in immune responses and prevent tissue damage. It is known that expression of TNF-α, which strongly activates NFκB, is itself up-regulated by NFκB. This provides a positive autoregulatory loop that amplifies the inflammatory response and perpetuates chronic intestinal inflammation [76]. For this reason, therapeutic intervention against TNF-α or NFκB activation has been used for the treatment of IBD [77]. In fact, inhibition of NFκB activity has been suggested to be a major component of the anti-inflammatory activity of glucocorticoids and 5-amino-salicylic acid, both of which are frequently used for treatment of chronic intestinal inflammation [78]. Also an amelioration of water absorption and the disturbances in hydroelectrolytic transport ascribed to early downregulation of the inflammatory cascade by quercitrin and rutin has been recently reported [79].

Positive effects of flavonols on the vascular system (antithrombotic and atherosclerotic effects) can be helpful in the inflamed intestine improving its microcirculation.

Protein binding effect of quercetin is the most recently discovered one [80]. IBD is considered to be an autoimmune disorder (with shared genetic predisposition for IBD and celiac disease), demonstrating increased gut permeability even in unaffected relatives of people with CD [81]. This increased epithelial permeability may result in a breakdown in the first line of defense against commensal bacteria and this coupled with other genetic factors could lead to an increase in innate and adaptive immune responses to disease-related microbial antigens. MAG12, recently implicated in UC and celiac disease, encodes a scaffolding protein involved in epithelial integrity (enabling protein-protein interactions) [82]. It is well known that bacterial metabolism of flavonoids occurs in the colon leading to their deglycosylation and further degradation into numerous phenolic and carboxylic acid products, though the biological significance of these products is still poorly understood. Other types of metabolites are those resulting from oxidation by reactive oxygen species as firstly recognized for quercetin [83]. It was also observed in human cell lines, and covalent binding of oxidized quercetin to DNA, but in particular to cellular protein was demonstrated [84]. It is proposed that this interaction with proteins might contribute to the biological action of flavonoids [81].

In summary, it seems that one of the most important beneficial effects of quercetin glycosides on IBD is their combined anti-inflammatory and immunomodulatory effect on intestinal epithelial cells suggesting that they may be an effective oral preventive and a therapeutic agent for this disease [73]. Their other effects, i.e. antithrombotic, atherosclerotic and cellular binding effects can contribute to their positive action on the inflamed intestinal tissue. Although the numerous studies published with *in vitro* approaches allow to identify molecular mechanisms of flavonols effects, the data obtained must be verified in humans and it is necessary to be very careful when extrapolating *in vitro* results to *in vivo* situations [60]. There are also differences between the mouse, rat and human gut with respect to the mechanism by which they utilize or exclude luminal flavonols [57]. In any case, the data nowadays available make clear the potential utility that flavonols have for the possible treatment of inflammatory

diseases. Considering reported observations, such as high concentration of administered flavonols in the colon, their binding to intestinal tissue, their deglycosylation by colonic bacteria, enterohepatic cycling, billiary excretion of quercetin glucuronides and their deglucuronidation in the inflamed tissue, local and systemic effects of quercetin metabolites and cellular protein binding effect, all these findings make rutin and quercitrin (and also quercetin in appropriate controlled release dosage form) promising candidates for the treatment of IBD. Their natural origin and absence of side effects can even make these substances more interesting with respect to IBD lifelong treatment. Further investigations aimed on clinical effects of flavonols would be a good start point for their therapeutic use in humans.

This work was supported by the Research Project MSM 0021620822 and IGA VFU 253/2009/FaF.

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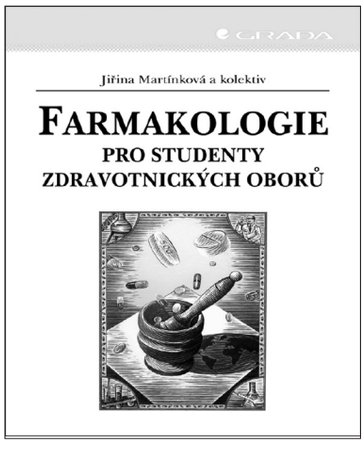

FARMAKOLOGIE - PRO STUDENTY ZDRAVOTNICKÝCH OBORŮ

Jiřina Martínková

Základní a dlouho očekávaná učebnice pro studenty zdravotnických oborů na lékařských a zdravotně sociálních fakultách i vyšších odborných školách. Text je doplněn mnoha grafy a praktickými příklady z praxe. Kniha obsahuje velké množství praktických poznatků, které potřebují členové interdisciplinárního zdravotnického týmu pro předepisování a podávání léků, sledování jejich účinků i edukaci pacienta.

Vydala Grada v roce 2007, šitá vazba, 380 stran, cena 379 Kč, 599 Sk, ISBN 978-80-247-1356-4.

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