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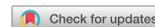
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Modifications of dietary flavonoids towards improved bioactivity: An update on structure–activity relationship

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ABSTRACT

Over the past two decades, extensive studies have revealed that inflammation represents a major risk factor for various human diseases. Chronic inflammatory responses predispose to pathological progression of chronic illnesses featured with penetration of inflammatory cells, dysregulation of cellular signaling, excessive generation of cytokines, and loss of barrier function. Hence, the suppression of inflammation has the potential to delay, prevent, and to treat chronic diseases. Flavonoids, which are widely distributed in humans daily diet, such as vegetables, fruits, tea and cocoa, among others, are considered as bioactive compounds with anti-inflammatory potential. Modification of flavonoids including hydroxylation, o-methylation, and glycosylation, can alter their metabolic features and affect mechanisms of inflammation. Structure–activity relationships among naturally occurred flavonoids hence provide us with a preliminary insight into their anti-inflammatory potential, not only attributing to the antioxidant capacity, but also to modulate inflammatory mediators. The present review summarizes current knowledge and underlies mechanisms of anti-inflammatory activities of dietary flavonoids and their influences involved in the development of various inflammatory-related chronic diseases. In addition, the established structure–activity relationships of phenolic compounds in this review may give an insight for the screening of new anti-inflammatory agents from dietary materials.

KEYWORDS

Anti-inflammation;
bioavailability; glycosylation;
hydroxylation;
O-methylation; flavonoids

Introduction

Polyphenols are widespread secondary metabolites throughout the plant kingdom (Pérez-Jiménez et al., 2010). They comprise a wide variety of molecules, characterized by a classic phenol ring structure (*i.e.* several hydroxyl groups in aromatic rings). Based on the number of phenol rings and the way they bond, polyphenols are divided into five categories (Fig. 1) including: flavonoids, tannins, phenolic acids, stilbenes and lignans (D'Archivio et al., 2007; Xiao and Högger, 2015b), since tannins are polymers of flavonoids and phenolic acids, Zamora-Ros et al. divided polyphenols into 4 main classes which are flavonoids, phenolic acids, lignans, and stilbenes (Zamora-Ros et al., 2014). Phenolic acid and flavonoids are regarded as the most abundant polyphenols in our daily dishes, and according to the degree of oxidation of the oxygen heterocycle, several classes have been divided, such as flavanols, flavonols, flavones, isoflavones, flavanones, anthocyanins, and proanthocyanidins (Cao et al., 2015; Zamora-Ros et al., 2016, Fig. 1). Both flavonols (or 3-hydroxy-flavones) and flavones are featured with an unsaturated benzo- γ -pyrone (A and C Rings) displaced to a

phenyl (B-ring) and as many as 7 hydroxyl groups surrounding their skeleton. As a result of numerous investigations, flavonoid with the position and number of hydroxyl groups to its chemical structure affected its biological activities (Xiao et al., 2013a, 2013b, 2015a, 2015b). Nowadays, polyphenols are used as a functional ingredient in foods preparations and dietary supplements. Due to their importance in food organoleptic properties and human health, a better understanding of their structures and biological activities would be of great help to reveal their further potential as therapeutic agents as well as for predicting and controlling food quality.

Inflammation is a defensive response to traumatic injuries and moderates the activation of inflammatory immune system, clearing pathogens and promoting tissue healing. However, an excessive inflammatory response may exacerbate self-injury and increase the incidence of many diseases and mortalities as well. The inflammatory response involves multiple disorders in signaling networks that normally regulate physiological homeostasis with the abnormal involvement of activation and/or inhibition of stimuli, resulting in the upregulation of cytokines,

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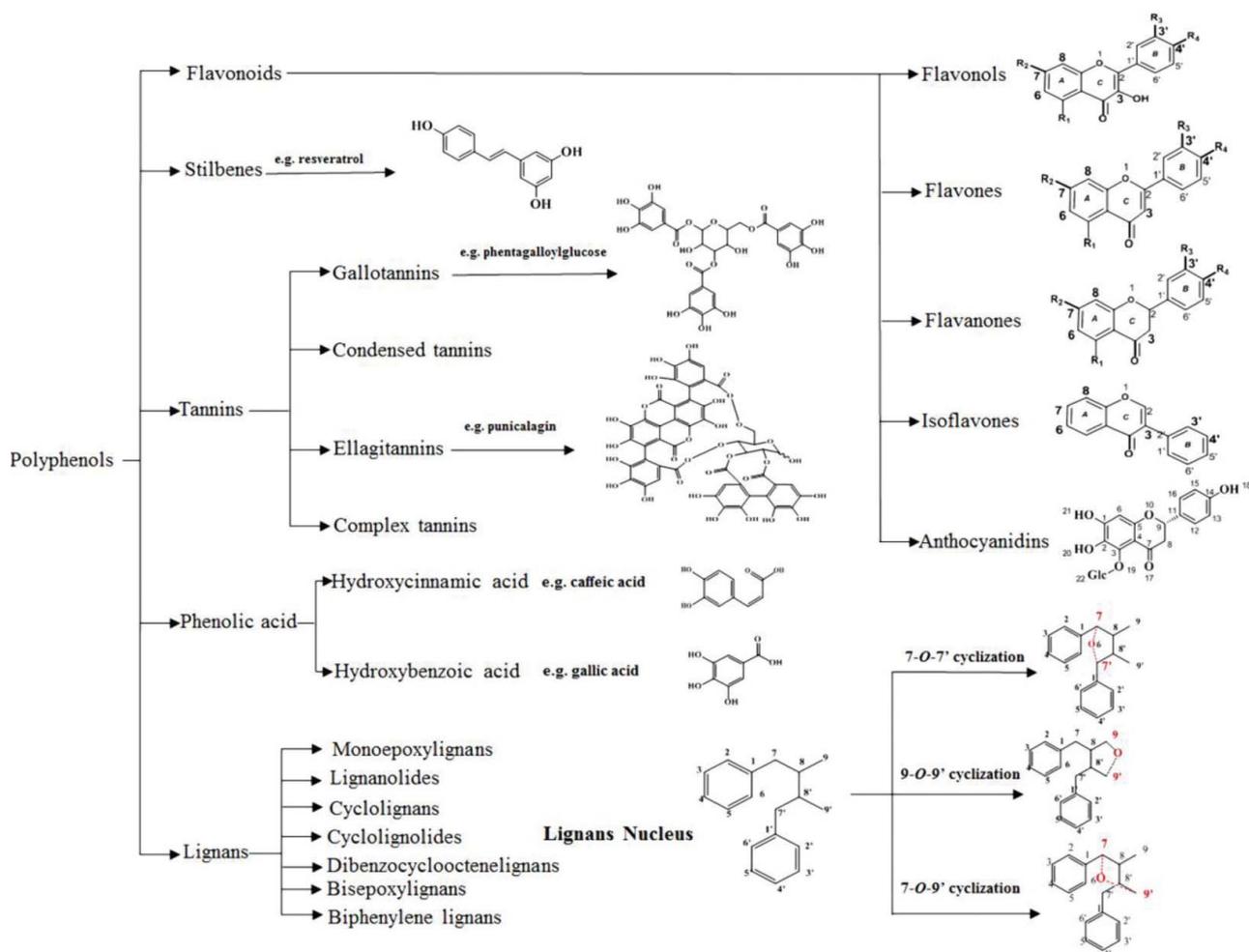


Figure 1. Polyphenol structures and classification.

chemokines, adhesion molecules, enzymes, receptors, and other proteins. Several mechanisms of action have been proposed aiming to explain the anti-inflammatory potential of phytoconstituents, including (Fig. 2): (1) antioxidant activity; (2) modulation of inflammatory cells (lymphocytes, macrophages, neutrophils, and mast cells); (3) modulation of proinflammatory activities of enzymes such as phospholipase A2 (PLA2), lipoxygenase (LOX), cyclooxygenases (COX), and nitric oxide synthase (NOS); (4) modulation of proinflammatory mediators; and (5) modulation of proinflammatory gene expression.

Studies showed that inflammation is associated with a wide range of progressive diseases, such as metabolic disorder, cancer, Alzheimer's and cardiovascular disease (Libby, 2007; Kiecolt-Glaser, 2010). Because of this, many studies have suggested that the prevention of various chronic diseases could be mediated by reduction or inhibition of chronic inflammatory mechanisms (Mestas and Ley, 2008; García-Lafuente et al., 2009; Pan et al., 2009). Further, epidemiological studies provide convincing evidence that natural dietary food components possess many beneficial biological activities. Among them,

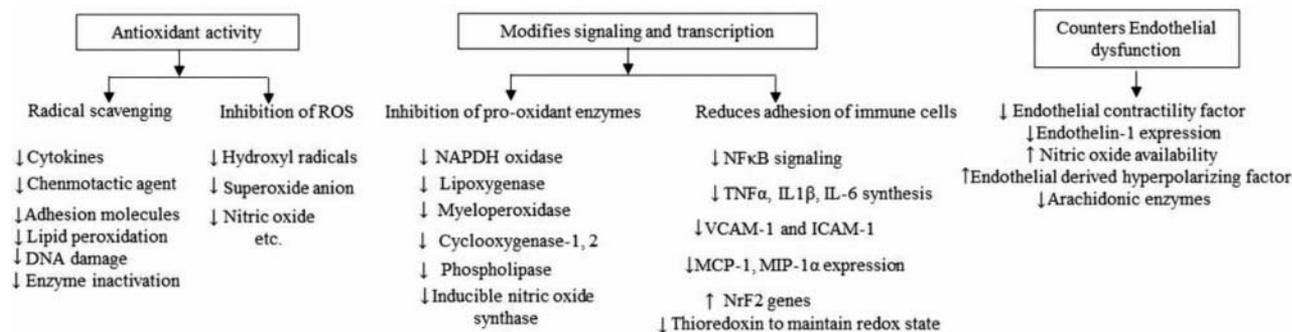


Figure 2. Several major mechanisms of anti-inflammatory action, including antioxidant activity, modulation of inflammatory cells, proinflammatory enzyme activities, proinflammatory mediators, and proinflammatory gene expression.

flavonoids are broadly well known for their pharmacological and biological functions, including antiviral, anticarcinogenic, antioxidant, antimicrobial, anti-inflammatory, antiangiogenic and antithrombogenic effects (García-Lafuente et al., 2009; Kiecolt-Glaser, 2010). Epidemiologic studies indicate that the incidence of chronic diseases and cancer is negatively related to the consumption of flavonoids enriched vegetables and fruits, which may attribute to their anti-inflammatory activities (Mennen et al., 2004). Normally, polyphenols in the daily diet are found as esters, glycosides or polymers which are not absorbed by human body directly, hence should be hydrolyzed by enzymatic reactions before absorption (Xiao et al., 2015a). Polyphenols could be metabolized by phase II enzymes in the cells of the small brush border and in the liver. A large proportion of polyphenol compounds presents several hydroxyl groups, which are enzymatically catalyzed by methylation, glucuronidation or sulfation. Polyphenol compounds are modified by these enzymatic reactions prior reaching the liver via the portal vein by active, passive or facilitated transportation. Some polyphenols could be absorbed until 50% such as isoflavones (Zamorano et al. 2014). However, only 5–10% of total polyphenol compounds are absorbed in the small intestine and these compounds may then undergo further extensive metabolism. Remaining polyphenols may accumulate in the large intestine and are subsequently excreted in the feces (Liu et al., 2017), most of these polyphenols will be transformed by the microbiota and absorbed as small phenolic acids. The consumption of polyphenol compounds may significantly be differentiated depending on the food nature. A major challenge nowadays is to discover the molecular basis of anti-inflammatory potential of flavonoids. Great attention should be paid on their effects of signaling pathways and molecular mechanisms involved in the inflammation and the potential to reduce and/or eliminate the burden of chronic inflammation-associated human diseases.

Bioavailability of polyphenols

It is important to point out that abundant consumption of polyphenols in humans daily diet does not bring as much effects as expected within the body, which may be due to a lower intrinsic activity or poor absorption in the intestine, high metabolism and rapid elimination. In addition, the metabolites found in blood and target organs which result from digestive or hepatic activity may differ from the native substances in terms of biological activity. Extensive knowledge of the bioavailability of polyphenols is, therefore, essential to understand their health effects. Bioavailability of polyphenols is affected not only by its ability to penetrate a membrane, but also by maintenance of their structural integrity. Dietary polyphenols are metabolized in the lumen of the small intestine, and then by the liver and other organs, where they undergo further modification (Lee, 2013). Moreover, some flavonoids (and related compounds) are not absorbed in the small intestine, but in the large intestine, hence a substantial structural modifications by colonic microflora occur. In addition to structure attributes of the nascent compound, the absorption, pharmacokinetics, biotransformation, and the relative activities of metabolites are critical determinants of biological effects in organisms.

In vitro data consistently demonstrate the biological efficacy of structurally diverse flavonoids under many circumstances of oxidative stress. However, the current understanding of absorption and metabolism in humans is limited to a small number of dietary flavonoids. All *in vitro* studies using aglycones or polyphenol-enriched extracts derived from plant foods have to be revisited and revised. All flavonoids from foods except for flavanols are found in glycosylated forms and glycosylation influences absorption. The fate of glycosides in the stomach is, however, not clear. In an interesting study, Crespy et al. (2002) reported that absorption of some flavonoids such as quercetin and daidzein is in stomach, but not for their glycosides. The aglycones are generated from their glycosides through bacterial hydrolysis with the release of sugar moiety, and it is widely believed that a limited absorption of some flavonoids like quercetin occurs only in the large intestine (Gee et al., 1998). Only aglycones and some glucosides can be absorbed in the small intestine, whereas polyphenols linked to a rhamnose moiety must reach the colon and be hydrolyzed by rhamnosidases of the microflora before absorption (Manach et al., 1995; Hollman et al., 1997). This may be similar for polyphenols linked to arabinose or xylose, even though this question has not been fully studied. Since absorption does not usually occur in the colon with a smaller exchange area and a lower density of transport systems compared to the small intestine, glycosides with rhamnose such as quercetin-3-rhamnoside (compound 49) are absorbed less rapidly and less efficiently than aglycones and glucosides. More direct evidences on the bioavailability of phenolic compounds have been given by experimental data measuring their concentrations in plasma and urine after the ingestion. For example, the maximum absorption occurs at 0.5–0.7 h after ingestion of quercetin 4'-glucoside by human but it requires 6–9 h to reach the maximum absorption for the same quantity of rutin (Graefe et al., 2001). Bioavailability and absorption kinetics also significantly vary in different sources, where a major difference among these sources is the type of glycoside (Hollman et al., 1997). Quercetin (from onions) with only glucosides is rapidly absorbed whereas the absorption of pure quercetin-3-rutinoside (from tea) shows a conspicuous delay. The absorption rates of a variety of glycosides from apples are intermediate. These results conform a predominant role of the sugar moiety in the bioavailability and absorption of dietary quercetin in the human body (Hollman et al., 1997). In the case of quercetin glucosides, absorption occurs in the small intestine and the efficiency of absorption is higher than that of aglycone (Hollman et al., 1995). Besides, the results imply the role of the colon in the absorption of quercetin rutinoside. The sugar moiety has a predominant effect on the absorption and plasma levels of quercetin. The underlying mechanism may partly elucidate that glycosylation enhances quercetin absorption. Hollman et al. (1995) suggested that glucosides can be transported into enterocytes by the sodium-dependent glucose transporter SGLT1. They can then be hydrolyzed at the inside of cells by a cytosolic-glucosidase (Day et al., 1998). Isoflavone glycosides present in soya products can also be deglycosylated by β -glucosidases from the human small intestine (Day et al.,

1998). However, the effect of glucosylation on absorption is less clear for isoflavones than for quercetin. Aglycones present in fermented soya products seem to be better absorbed than the glucosides ingested from soybeans (Hutchins et al., 1995). With the oral administration of pure daidzein, genistein, or their corresponding 7-glucosides to healthy volunteers, Setchell et al. (2001) showed that the systemic bioavailability of genistein was much greater than that of daidzein and the bioavailability of these isoflavones was greater when ingested as β -glycosides rather than aglycones. However, in another human study, peak of plasma concentrations was significantly higher after aglycone ingestion than glucoside ingestion, which was observed with either low or high single doses or long-term intakes (Izumi et al., 2000). In addition, hydrolysis of isoflavone glycosides into aglycones in a soy drink does not change the bioavailability of the isoflavones in humans (Izumi et al., 2000). Analysis of ileal fluid collected from ileostomists after the ingestion of various foodstuffs indicate that even when dietary flavonoids are absorbed in the small intestine, substantial quantities none-the-less pass from the small to the large intestine (Jaganath et al., 2006) where the colonic microbiota will cleave conjugating moieties and the resultant aglycones will undergo ring fission leading to the production of smaller molecules, including phenolic acids and hydroxycinnamates. These can be absorbed and may be subjected to phase II metabolism in the liver before being excreted in urine in substantial quantities that, in most instances, are well in excess of the flavonoid metabolites that enter the circulatory system via the small intestine (Stalmach et al., 2010). The intestinal absorption of polyphenols can be high. However, the plasma concentration of any individual molecule rarely exceeds 1 μ M after the consumption of 10–100 mg of a single compound. Measurement of the plasma antioxidant capacity suggests that more phenolic compounds are present, largely in the form of unknown metabolites, produced either in our tissues or by the colonic microflora. It will be important to learn more about these metabolites, particularly because of their potent biological activity. Biologists should focus less on the parent compounds as they are ingested and more on the biological activities of the

metabolites present in our tissues, and in particular on the conjugated analogues.

O-methylation

O-Methylation is commonly used in the synthesis of secondary metabolites in plants and micro-organisms, by which methyl groups are transferred to hydroxyl groups of the recipient compound in order to increase the hydrophobicity of the latter molecule (Kim et al., 2006a, 2006b). After several O-methylation reactions, flavonoid derivatives from plants broaden the repertoires against environmental stimuli and play a role in plant growth and development (Frick et al., 2001). Tewtrakul et al. (2009) evaluated the compounds isolated from the rhizomes of *Kaempferia parviflora* Wall. ex Baker (Zingiberaceae) by examining their inhibitory activities against nitric oxide (NO) production. Results showed that 5-hydroxy-3,7,3',4'-tetramethoxyflavone (compound 3) expressed the highest NO inhibitory activity with an IC_{50} of 16.1 μ M, followed by 5-hydroxy-7,4'-dimethoxyflavone (compound 5) (IC_{50} = 24.5 μ M) and 5-hydroxy-3,7,4'-trimethoxyflavone (compound 4) (IC_{50} = 30.6 μ M), while other compounds showed moderate to weak potential. The NO inhibition activity of compound 5 (IC_{50} = 16.1 μ M) was 3 times weaker than that of caffeic acid phenylester (an NF- κ B inhibitor, IC_{50} = 5.6 μ M), but 4 times higher than L-nitroarginine (a NOS inhibitor, IC_{50} = 61.8 μ M). The structure–activity trends of *K. parviflora* upon NO inhibition can be summarized as follows: 4'-methoxyl group attached to B-ring increased the activity, as shown in compound 4 (IC_{50} = 24.5 μ M) versus compound 2 (IC_{50} = 64.3 μ M); and nearby methoxylation at positions 3' and 4' brought a higher activity as observed in compound 5 (IC_{50} = 16.1 μ M) versus compound 3 (IC_{50} = 30.6 μ M) (Tewtrakul et al., 2009). The extract from *Geranium robertianum* L. (Geraniaceae) bark is widely used as a traditional Peruvian medicine for treatment of different malignancies (Elmadfa and Wagner, 2008), arthritic pain and gastritis, which activities are likely due to its anti-inflammatory and antioxidant properties by inhibiting tumor necrosis factor (TNF)- α production and

Table 1. *In vitro* anti-inflammatory actions and pathway of some major aglycone in dietary foods.

Example	Action	Pathway	References
Apigenin	\downarrow NO, \uparrow NF- κ B: \uparrow IKK, \downarrow I κ B, \uparrow MAPKs, \downarrow proteasome activity, \downarrow COX-2, \downarrow PGE2, \downarrow IL-6	p65 translocation to the nucleus, DNA binding transcriptional activity; p38 MAPK, ERK and JNK enzyme activity; VCAM-1, ICAM-1 expression	Liang et al., 1999; Chen et al., 2004; Choi et al., 2004; Chen et al., 2005; van Meeteren et al., 2004
Luteolin	\downarrow NO, \uparrow NF- κ B: \uparrow IKK, \downarrow I κ B, \uparrow MAPKs, \downarrow proteasome activity, \downarrow COX-2, \downarrow PGE2, \downarrow IL-6,	TNF- α release, p38 MAPK and ERK pathways, VCAM-1, ICAM-1 and E-selectin expression, cJun phosphorylation cJun and cFos mRNA levels DNA binding transcriptional activity	Choi et al., 2004; Hirano et al., 2006 Byun et al., 2010; Shichijo et al., 2003
Quercetin	\downarrow NO, \uparrow NF- κ B: \uparrow IKK, \downarrow I κ B, \uparrow MAPKs, \downarrow proteasome activity, \downarrow COX-2, \downarrow PGE2, \downarrow IL-6, \downarrow IL-8, \downarrow IL- β , \downarrow CXCL2, \downarrow CCL5	TNF- α release, p38 MAPK and ERK pathways, VCAM-1, ICAM-1 and E-selectin expression, cJun phosphorylation cJun and cFos mRNA levels DNA binding transcriptional activity	Comalada et al., 2005; Hämäläinen et al., 2011; Min et al., 2007
Chrysin	\uparrow NF- κ B, \downarrow I κ B	DNA binding transcriptional activity	Hougee et al., 2005
Kaempferol	\downarrow NO, \uparrow NF- κ B: \uparrow IKK, \downarrow I κ B, \uparrow MAPKs, \downarrow proteasome activity, \downarrow COX-2, \downarrow PGE2, \downarrow IL-6,	DNA binding transcriptional activity, p38 MAPK and ERK pathways	Hämäläinen et al., 2011; García-Mediavilla et al., 2007
Myricetin	JAK1/STAT 3	Syk activity	Wang et al., 2010;
Catechin	\uparrow NF- κ B, \uparrow IKK, \downarrow COX-2	P50 translocation to the nucleus, DNA binding transcriptional activity, TNF- α release	Suzuki et al., 2007; Hirao et al., 2010

prostaglandin modulation (Piscoya et al., 2001; Sandoval et al., 2002). Three flavonoids have been identified in *G. robertianum* extract: 3',4'-dimethoxyflavone (compound 9), homoeriodictyol (compound 10) and kaempferol (compound 11). The former 2 compounds both have a C2 = C3 double bond and a 4-oxo group; nevertheless, the orthocatechol group has one or two methylated OH groups that may lead to the decreased antioxidant activity (Cao et al., 1997). Compound 11, though only one OH group is stuck to the B-ring, is known as a potent antioxidant because it exhibits the C2 = C3 double bond and the 5-OH and 3-OH groups with the 4-oxo group on the C-ring (Amaral et al., 2009). High antioxidant potential of these compounds might justify their effectiveness for inflammatory diseases treatment and certain types of neoplasms, as far as the inflammation is a trigger for their development. Chrysin (5,7-dihydroxyflavone, compound 12) is a natural flavonoid abundantly found in blue passion flower, propolis, fruits, and vegetables (Sobocanec et al., 2006). Previous studies highlighted chrysin (Table 1) an anti-inflammatory molecule by inhibiting several cytokines, such as COX-2, prostaglandin E2 (PGE2), and NO (Ha et al., 2010; Harasstani et al., 2010). Although chrysin showed many beneficial effects in *in vitro* studies, its absorption after oral administration either in animals or humans is low, because of rapid metabolism in small intestine and liver (Walle et al., 1999). Methylation, glucuronidation, sulfation, and ring-fission metabolism represent the major metabolic pathways for flavonoids. However, O-methylation would eventually make flavonoids metabolically more stable and also would increase their bioavailability as well as a higher tissue distribution than unmethylated forms (Wen and Walle, 2006; Walle et al., 2007). For instance, 5,7-dimethoxyflavone (compound 13) and 5,7,4-trimethoxyflavone (compound 14) both were found ten times more effective in inhibiting the proliferation of human oral squamous SCC-9 cancer cell line (IC₅₀ values 5–8 mM) than the corresponding unmethylated analogs apigenin (compound 15) and chrysin (Walle et al., 2007). In particular, O-methylation ensures a superior anticancer activity as compared with the corresponding hydroxylated derivatives, since it is more resistant to the hepatic metabolism and shows a higher intestinal absorption (Bernini et al., 2011). As it is known, very limited studies have been dedicated to the oral bioavailability of other polymethoxyflavones or methoxyflavones. One related study administered nobiletin (compound 16, polymethoxyflavonoid) and unmethylated luteolin (compound 17, 5,7,3',4'-tetrahydroxyflavone) to rats at a dosage of 25 mg/kg, which found that significant amounts of nobiletin were detected in the whole liver and kidney specimens, but accumulation of luteolin was in traces (Murakami et al., 2002). Another polymethoxyflavone, tangeretin (compound 18, 5,6,7,8,4'-pentamethoxyflavone) was blended to hamsters' diet with 1% dosage and administered for 35 days, and urinary excretion of animal metabolites indicated that a considerable amount of tangeretin was absorbed in the intestine. However, changeable tangeretin was detected in plasma (Kurowska and Manthey, 2004). Several methylated flavones, involving compound 13, 7-methoxyflavone

(compound 19), and 7,4'-dimethoxyflavone (compound 20), showed higher intestinal absorption and metabolic resistance than their unmethylated analogs (Ta and Walle, 2007). Recently, Sae-Wong et al. (2011) have showed that compound 13, trimethylapigenin (compound 21), and tetramethyluteolin (compound 22) significantly inhibited NO production in lipopolysaccharide (LPS)-activated RAW264.7 macrophage cells (IC₅₀ values of 5.1, 4.6, and 8.7 μg/mL, respectively); whilst 3,5,7-trimethoxyflavone (compound 23), 3,7,4'-trimethylkaempferol (compound 24), and ayanin (compound 25) possessed moderate to mild activity (IC₅₀ = 44–60 μg/mL). In an earlier study, Matsuda et al. (2003) checked the effects of 73 different flavonoids on NO production in LPS-activated peritoneal macrophages from mouse and clarified structure–activity relationship of flavonoids for the inhibition of NO production: (a) strongly active flavonoids possessed 5,7-dihydroxyl group and C2-C3 double bond; (b) kaempferol (compound 11) < quercetin (compound 31) < luteolin (compound 17), tamarixetin (compound 28) < ombuine (compound 29) < pilloin (compound 32) (Kim et al., 1999a, 1999b; You et al., 1999). Flavonoids exhibit the anti-inflammatory activity partially related to their inherent antioxidant capacity. The scavenging ability of flavonoids is due to the existence of double bond between carbons 2 and 3 in the C-ring of flavonoid skeleton (Bonfili et al., 2008). Methylation of the 3-hydroxyl group also exhibited a higher inhibition against NO production such as: rhamnetin (compound 27) < lzalpinin (compound 26), ombuine (compound 29) < ayanin (compound 25) (Soobrattee et al., 2005). Similarly, methylation of the 5-hydroxyl group enhanced the activity (Plochmann et al., 2007): compound 33 < compound 34 and 7-penta-O-methyl quercetin (compound 30); and methylation of the 4'-hydroxyl group also improved the activity (Mastuda et al., 2002): luteolin (compound 17) < diosmetin (compound 35), and quercetin (compound 31) < tamarixetin (compound 28). In addition, Mastuda et al. (2003) reported that the flavones with the 5-hydroxyl moiety exhibited a stronger NO inhibitory effect than those without it, as for example: 7-hydroxyflavone < chrysin, 4',7'-dihydroxyflavone < apigenin, and 3',4',7'-trihydroxyflavone < luteolin (Table 1). However, flavonols and flavones with the 4'-hydroxyl group exhibited stronger activities than those with 3',4'-dihydroxyl moiety and lack of the hydroxyl group at the B ring (Mastuda et al., 2003). Flavonols having the 3',4'-dihydroxyl group showed higher activities than those having the 3',4',5'-trihydroxyl group: compound 37 < tamarixetin (compound 27), myricetin (compound 36) < quercetin (compound 31), compound 38 < rhamnetin (compound 27), and compound 39 < luteolin. Comparison between flavones and flavanones suggested that the C2-C3 double bond moiety improved the activity: flavanone < flavone, liquiritigenin (compound 43) < compound 12, and eriodictyol (compound 45) < compound 17. The 4'-or 3',4'-vicinal substitutions and 8-methoxyl group positively enhanced inhibitory activity, and the 2',4'-hydroxyl substitution abolished the inhibitory activity. However, the 3-hydroxyl moiety decreased the activity. Besides, potent NO inhibitors were discovered to inhibit iNOS induction with no inhibitory activity toward iNOS enzymatic activity

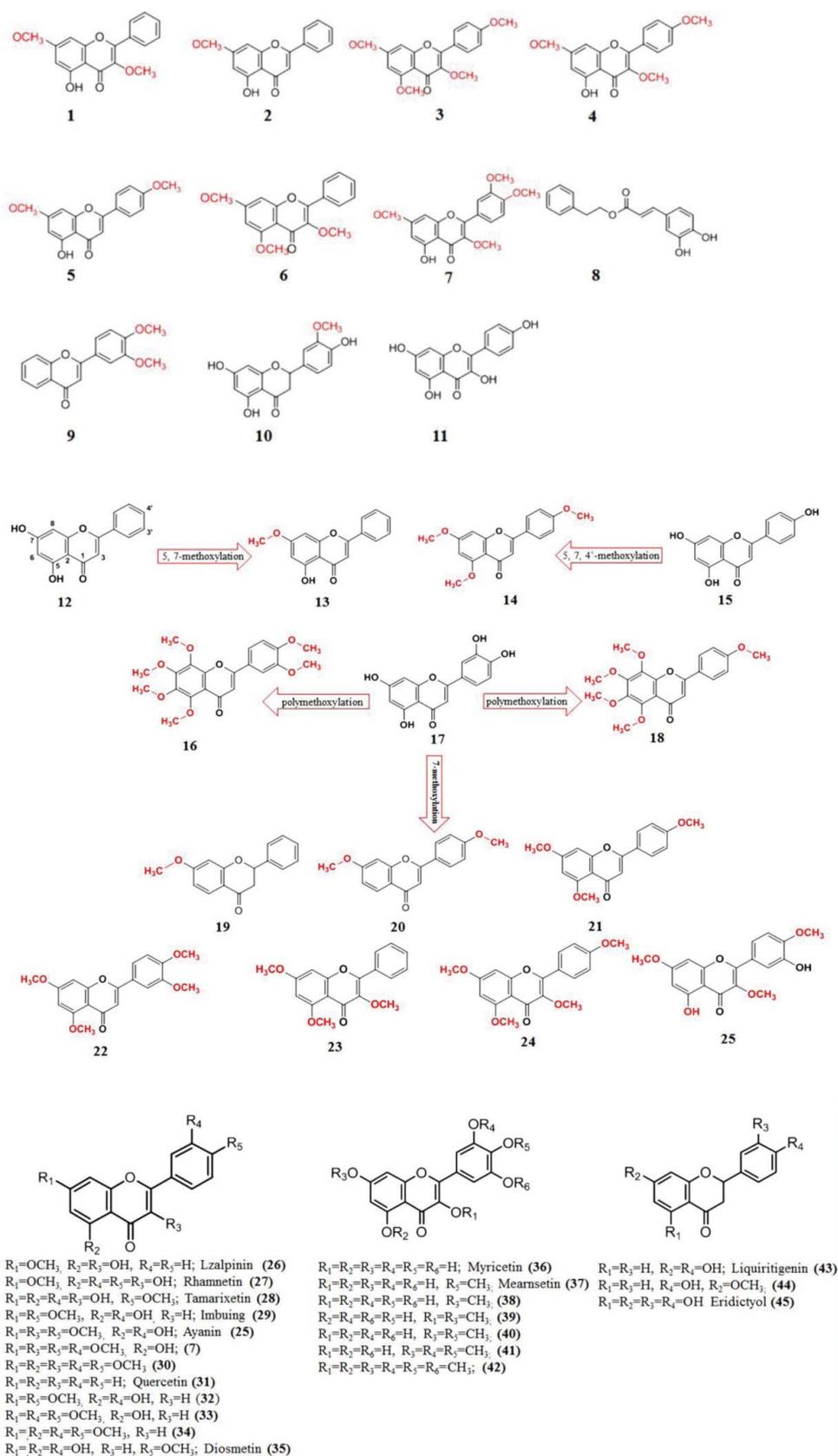


Figure 3. The structure of methylated flavonoids.

(Sae-Wong et al., 2011). The inhibition of enzymes and NO production involved in the production of prostaglandins and leukotrienes, is also correlated to the double bond between C_2 and C_3 (Kim et al., 2004). In a similar study, the presence

of the $C_2 = C_3$ double bond in C-ring is required for the optimal intercellular adhesion molecule-1 (ICAM-1) expression inhibition (Benavente-Garcia et al., 2008). The potential methylation sites of flavonoids affecting the anti-

inflammatory effect are shown [Figure 3](#). Evidence presented above indicated that *O*-methylation of flavonoids could increase their bioavailability as well as to improve their chemopreventive properties

Hydroxylation

The hydroxylation of A-ring of flavonoids, especially for 5- and 7-hydroxylations, is beneficial for antioxidant activity (Bonfili et al., 2008), inhibition of NO production (Kim et al., 1999a, 1999b) and expression of cell adhesion molecules such as ICAM-1 (Teng and Chen, 2016). Ring hydroxylation has been reported to be critical in improving COX-2 inhibition in A549 cell line (Tjendraputra et al., 2001). In addition, their potency is also found to be associated with the form and number of hydroxylations on the A/B-ring (Pelzer et al., 1998); as shown in [Table 2](#), the 5- and 7-hydroxylations on the A-ring and 4'-hydroxylation on the B-ring are the most frequently occurring. The hydroxyl group at position 3 on the C-ring slightly blocks the ICAM-1 expression (Chen et al., 2004). The inhibition of TNF- α production is likely to require a structure of 5- and 7-hydroxyflavones which is prevalent in apigenin and luteolin (Ueda et al., 2004). In addition, 8-methoxyl group on the A-ring favorably influences the inhibition of NO production (Kim et al., 1999a, 1999b). Subclasses of flavonoids including flavonols, flavanones, flavones, and isoflavones were systematically investigated for PGE2 production inhibition (Takano-Ishikawa et al., 2006). Results suggest that the 4-oxo on the C-ring is crucial for a higher inhibitory effect and the C2-C3 double-bond improves the activity. It has been further revealed that the C2-C3 double bond reduction led to a decrease in the inhibitory activity

of the COX pathway, essential for PGE2 production (Landolfi et al., 1984). The inhibitory activities of flavonoids seem to be determined by the number and position of hydroxyl residues. Among the checked inhibitory flavonoids, the presence of 5- and 7-OH got higher activities than those with only 7- or without 5- and 7-OH (Burda and Oleszek, 2001; Yoon et al., 2013). Morin (3,5,7,2',4'-pentahydroxyflavone), administered orally at a dose 25 mg/kg daily, has been reported to exert inhibitory effect against the level of interleukin (IL)-1 β in chronic experimental colitis in rats and significant decrease was noticed after 3 weeks (Galvez et al., 2001). Harasstani et al. (2010) reported that Morin *in vitro* studies inhibits the TNF- α and IL-4 levels in IgE-primed RBL-2H3 cells (Harasstani et al., 2010). On the other hand, Morin suppressed the production of NO and PGE2 in LPS-stimulated RAW 264.7 cells with IC₅₀ values equal to 17.47 and 44.85 μ M, respectively. It should be noticed that quercetin (3,3',4',5,7-pentahydroxyflavone dihydrate), the most common flavonoid compound synthesized in plant, *in vitro* study, at a dose of 100 μ M, significantly inhibited the production of PGE2 in rheumatoid synovial fibroblast (Sung et al., 2012). As regard to the possible inhibitory mechanism, one conceivable proposal is that several flavonoids like quercetin potently suppress protein tyrosine kinase. The results on flavonols and flavone showed that compounds without a -OH residue on the B-ring were more effective than those with 3'- and 4'-OH, but more than two hydroxyl residues on the B-ring caused a loss of inhibitory activity. In isoflavones, compounds with 5-OH residue were more effective than those without 5-OH. The hydrophobicity of the flavonoids which impacts its permeability is decided by the coordination of sugars as well as the hydroxyl residues number.

Table 2. Hydroxylation of flavonoids for inhibitory effect on PGE2 biosynthesis in rat peritoneal macrophage stimulated by LPS.

	Name	Example	Site	Effect	References		
Flavonols	3-Hydroxyflavone	→7-Hydroxyflavonol	→3, 7	↑*	Burda and Oleszek, 2001		
		→Galangin	→3, 5, 7	↑	Xia et al., 2013		
		→Kaempferol	→3, 5, 7, 4'	↑*	Yoon et al., 2013		
		→Fisetin	→3, 7, 3', 4'	↓**	Suh et al., 2009		
		→Wogonin	→5, 7	↓	Suh et al., 2009		
		→Morin	→3, 5, 7, 2', 4'	↓**	Chen et al., 2012; Harasstani et al., 2010		
		→Quercetin	→3, 5, 7, 3', 4'	↑	Sung et al., 2012		
		→Isorhamnetin	→3, 5, 7, 4'	↓**	Takano-Ishikawa et al., 2001		
		→Robinetin	→3, 7, 3', 4', 5'	↓**	Takano-Ishikawa et al., 2001		
		→Quercetagenin	→3, 5, 6, 7, 3', 4', 5'	↓**	Ferrandiz and Alcaraz, 1991		
		→Myricetin	→3, 5, 7, 3', 4', 5'	↓**	Medeiros et al., 2008		
		Flavanones	Naringenin	→Eriodictyol	→5, 7, 3', 4'	↑	Folmer et al., 2012
				→Hesperetin	→5, 7, 3'	↓**	Do et al., 2014
				→Hesperidin	→5, 3'	↓**	Sakata et al., 2003
Flavones	5-Hydroxyflavone	→7-Hydroxyflavone	→7	↑	Takano-Ishikawa et al., 2001		
		→Chrysin	→5, 7	↑	Saadawi et al., 2012		
		→Baicalein	→5, 6, 7	↑	Nakahata et al., 1998		
		→Apigenin	→5, 7, 4'	↑	Suou et al., 2011		
		→7,3',4'-Trihydroxyflavone	→7, 3', 4	↓*	Takano-Ishikawa et al., 2001		
		→Luteolin	→5, 7, 3', 4'	↓**	Wang et al., 2007		
		→Luteolin	→5, 7, 3', 4'	↓**	Wang et al., 2007		
Isoflavones	Daidzein	→Daizin	7,4'→4'	↓**	Takano-Ishikawa et al., 2001		
		→Genistin	→5, 4'	↑*	Hämäläinen et al., 2011		
		→Genistein	→5, 7, 4'	↓**	Horia and Watkins, 2006		
		→Genistein	→5, 7, 4'	↓**	Horia and Watkins, 2006		

↑indicated increased activity; ↓indicated decreased activity;

*significant difference at $p < 0.05$;

**significant difference at $p < 0.01$

C2=C3 double bond in combination with 3-OH

In fact, for most flavonoids, due to the presence of C2=C3 double bond, the OH-linked to the C3 position can easily occur monoelectronic oxidation to produce a hydroxyl radical, and unpaired electrons can delocalize in C2 and B ring. In numerous studies, the role of the C2=C3 double bond and 3-OH group were discussed. Most studies acknowledged the importance of C2=C3 double bond since it contributes to the antioxidant activity of flavonoids (Robak and Gryglewski, 1987; Ratty and Das, 1988; Cholbi et al., 1991). Recently, Gregoris and Stevanato (2010) found that radical scavenging activities of galangin (OH at C3) and apigenin (OH at C4') were associated with unpaired electrons in different positions on B aromatic ring and the galangin with OH attached at C3 expressed a much higher antioxidant activity than apigenin with OH attached at C4'. According to previous studies, a general agreement was achieved that the presence of OH groups with a preference for a catechol moiety in ring B is crucial, conferring a high stability to the aroxyl radical via expanded electron delocalization (Bors et al., 1990b) or hydrogen bonding (Bors et al., 1990a). Naringenin without the C2 = C3 double bond showed a low antioxidant capacity, but a high antioxidant capacity was found in kaempferol with the double bond in C2 = C3 and the hydroxyl group in C3 (Gregoris and Stevanato, 2010). This is probably caused by a combination of the C2 = C3 double bond with the 3-OH, which also turns flavonols and flavones into better scavengers than the flavanols and flavanones. Similarly, Burda and Oleszek (2001) looked for a link between the structure of 42 flavonoids and their antioxidant and antiradical activities; and results showed that only flavonols with a free hydroxyl group on C3 position presented a high inhibitory activity to β -carotene oxidation, and that antiradical activity depended on the presence of C2 = C3 double bond and free hydroxyls on C3. Despite both C3 and C4' radicals can delocalize the unpaired electron on the C2 = C3 double bond and the aromatic ring, antioxidant properties are quite different. Rigobello et al. (2004) explained this phenomenon as the steric hindrance of C3 hydroxyl group stabilized the radicals. Similar conclusion was drawn for artemillin C, which consists of a phenolic structure with a strongly obstructed hydroxyl group (Kumazawa et al., 2004). It seems that the C2=C3 double bond is more important than the keto group for the antioxidant properties. In fact, no reasonable formulas for resonance limit involve the keto group in the formation of C3 phenoxyl radical. Kumazawa et al. (2004) found low 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical scavenging activity for pinobanksin which contains a hydroxyl group in C3 and the keto group in C4, but not the C2=C3 double bond. Hydroxyl groups placing into the molecular structure affect antioxidant properties of the molecule more than the generic number of the hydroxyl groups (Wu et al., 2007). It is possible to state that in benzenic structures, the presence of two hydroxyl groups to ring position confers elevated antioxidant properties to its molecule, such as a hydroxyl group in C3 connected with the C2=C3 double bond conjugated to the aromatic ring in the flavonoid structure. High

inhibitory effect against aldose reductases is attributed to the molecules with a C2=C3 double bond, which allows the formation of a high *p*-conjugation for linking B and C rings (Xiao et al., 2015a). Moreover, isoflavones do not form H-bonds within the catalytic residues of human salivary α -amylase, which is a likely consequence of the ring B position; in isoflavones, as contrary to the other flavonoids, the B-ring is attached to carbon C3 rather than C2 of ring C (Piparo et al., 2008). Hydrogenation of the C2 = C3 double bond for many flavonoids weakens the binding affinity for α -amylase by 2–4 orders of magnitude (Xu et al., 2016). Tadera et al. (2006) reported that the inhibitory effect of apigenin with an inhibitory percentage of 21% was stronger than naringenin (5%) against porcine pancreatic α -amylase. In fact, flavonols with C2 = C3 double bond show a planar structure of sp^2 , and then trigonal planar, the electronic configurations of all the carbon atoms. The oxygen atom, alone, does not alter this planar configuration. Planarity of the C ring in flavonoids could play a very important role in binding interaction with proteins, as the molecules with saturated C2 = C3 bonds (flavanones and certain others) permit increased twist of the B ring with reference to the C ring. The molecules with near-planar structure easily enter the hydrophobic pockets in enzymes. The missing electrons lead to weaker π - π interactions with the indole ring of Trp59, eventually, leading to a reduced inhibitory activity of these compounds toward human salivary α -amylase. Furthermore, flavonoids with a C2 = C3 double bond are more effective than the corresponding homologues (comparison of flavone with flavanone, chrysin with pinocembrin, and quercetin with eriodictyol) on ethoxyresorufin *O*-deethylase and *O*-debenzylase (Siess et al., 1995). Similar results were obtained by analyzing other enzyme inhibitory effects including: α -glucosidases (Xiao et al., 2015a), angiotensin-converting enzyme (Guerrero et al., 2012), and other enzymes implicated in carcinogen activation (Weidmann, 2012). In summary, previous study indicated that saturation of the C2 = C3 double bond decreased enzyme inhibitions. It has been reported that reduction of the C2 = C3 double bond leads to reduced suppressions of the COX pathway and PGE2 production (Landolfi et al., 1984). In another study, a similar tendency was observed for the inhibition of COX-1 and COX-2 (Takano-Ishikawa et al., 2006). The C2 = C3 double bond in conjugation with a 4-oxo group plays a very important role for the affinity of common human plasma proteins. In addition, naringenin (flavanone), which lacks the C2 = C3 double bond of apigenin, does not inhibit insulin-stimulated glucose uptake, suggesting that the C2 = C3 double bond also plays an important role in insulin-stimulated glucose uptake in MC3T3-G2/PA6 adipose cells (Nomura et al., 2008). Flavanols, (+)- and (-)-catechin, which do not possess a C2 = C3 double bond, don't show any effect on glucose uptake. The presence of a C2 = C3 double bond in flavones and flavonols is suggested to be critical for inhibitory activity against protein kinases, including phosphoinositide 3-kinase (PI3K), phospho kinase C (PKC), myosin light chain kinase and G type casein kinase (Jinsart et al., 1991; Agullo et al., 1997; Chen and Kang, 2013). Conclusively, the results suggest that C2

= C3 double bond in dietary phenolic compounds significantly enhances their various biological effects. Understanding the structure–activity relationship will ultimately contribute to a better comprehension of the variable results of epidemiological studies in different populations, and will allow us to make a more qualified statement about the impact of food on health. The C2 = C3 double bond is, therefore, a promising modification approach to provide optimum biologic activity of flavonoids and allow novel applications.

Glycosylation

As mentioned above, most flavonoids in plants appear as glycosides, and some are presented in aglycone (lack of sugar moiety). At least eight different monosaccharides or their combined forms (di- or trisaccharides) can bind to different hydroxyl groups of the flavonoid aglycone (Williams and Harborne, 1986; Chen and Kang, 2014a; Chen et al., 2014b). A great number of flavonoids are derived from different combinations of flavonoid aglycones and these sugars (Figure 4). The glycosides usually include β -D-glucopyranosyl (Glc), β -D-glucopyranosiduronic acid (GlcA), α -L-rhamnopyranosyl (Rha), neohesperidosyl (Neo), or Glc (6 \rightarrow 1) Rha (Rut) (Xiao et al., 2015a). Glycosylation generally occurs in the metabolism of flavonoids, and flavonoid glycosides have been shown to possess higher-hydrophilic properties than aglycones form (Lin et al., 2005; Chen et al., 2016). Kim et al. (2009) reported that flavonoid glycosides were metabolized to aglycones by human intestinal microflora, producing α -rhamnosidase, exo- β -glucosidase, endo- β -glucosidase, and β -glucuronidase. Accordingly, rutin, hesperidin, naringin, and poncirin were transformed to their respective aglycones with arhamnosidase and β -glucosidase produced by intestinal bacteria (Kim et al., 1999a, 1999b). The *in vitro* hydrolytic capability of α -rhamnosidases on flavonoid glycosides varied with pH and temperature, and indicated compound properties in a reaction buffer (Hollman and Katan, 1998). Flavonoid glycosides (rutin and quercitrin) exhibited a significant NO inhibition *in vivo* but were ineffective in LPS-stimulated macrophages *in vitro*; while flavonoid aglycone (quercetin) showed NO inhibitory effect both *in vivo* and *in vitro* (Shen et al., 2002). Taken together, these data indicate that *in vivo* metabolic activity to convert flavonoid glycosides into aglycones may be necessary for their NO inhibitory activities. However, the direct evidences are still insufficient.

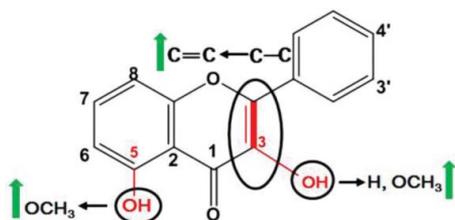


Figure 4. The potential methylation sites of flavonoids affecting the anti-inflammatory effect. The green up arrows represent increasing the effect.

O-glycosylation

Flavone O-glycosides are composed of aglycone moieties with one or more sugars attached *via* β -linkage. These compounds may be modified by endogenous enzymes like malonyltransferases (conversion from malonylapiin to apiin) (Shanmugam et al., 2008). For many flavonoid glucosides, β -glucosidase activity in brush border of small intestine is sufficient to hydrolyze the aryl glycosidic bond and allow the aglycone absorption. Intestinal β -glucosidase, however, cannot hydrolyze oligosaccharide moieties. Previous studies using fluorescent microscopy or HPLC analysis showed that flavonoid aglycones, rather than glycosides, are transported into hepatocytes to finally accumulate in the nucleus (Kanazawa et al., 2006). Although intestinal bacteria can cleave these bonds, absorption is reduced. As long as dietary flavones are ingested predominantly as glycosides, their biological effect are depended on how and where they are hydrolyzed, absorbed, metabolized, transported, and excreted. Flavone glycosides in celery present as apiosylglucosides and might also be resistant to brush border β -glucosidase action.

The glycosylation also plays an important role in biological action of flavonoids (Xiao, 2016). For instance, flavonoid aglycones are more potent than corresponding glycosides (diosmetin *vs.* diosmin) (Benavente-Garcia et al., 2008). The flavonoid glycosides may not penetrate the cell membrane due to their hydrophilicity, or there might be steric impediment due to their large glycosyl residues (Kim et al., 1999a, 1999b). However, glucoside acetylation may facilitate the availability of the flavonoids to suppress TNF- α expression (Shie et al., 2010). Finally, prenylated flavonoids that inhibit COX-2 activity all have a C3 isoprenyl residue in their structures (Kim et al., 2004). Substantial quantities of quercetin-3,4'-di-O-glucoside (compound 48) and quercetin 4'-O-glucoside are discovered in onions (Rhodes and Price, 1996) along with lower levels of quercetin 3-O-glucoside as reported by Gee et al. (1998). Isoquercitrin (quercetin 3-glucoside, compound 46) showed higher anti-inflammatory effect in their glycosides than the respective aglycone (quercetin) in a murine model of asthma (Rogerio et al., 2007). Previous studies also showed that quercetin 3-O-rhamnoside (compound 49) from *Houttuynia cordata* possessed a strong anti-inflammatory capacity through the inhibition of epithelial cell activation during chronic intestinal inflammation. Apparently, quercetin 3-O-galactopyranoside (compound 53), quercetin 3-O-arabinopyranoside (compound 50), quercetin 3-O-rhamnopyranoside (compound 52), myricetin 3-O-glucoside (compound 54) were confirmed as potential anti-inflammatory agents in carrageenan-induced rat paw edema (Mothana et al., 2012).

Moreover, a number of studies have proved that epigallocatechin gallate (EGCG, compound 55) inhibits LPS-induced microglial activation and protects against inflammation-mediated dopaminergic neuronal injury (Li et al., 2004; Cavet et al., 2011; Zhong et al., 2012). Theaflavins from black tea have been suggested to reduce oxidative stress and inflammation by their radical scavenging ability and downregulation of pro-inflammatory mediators both *in vitro* and *in vivo* (Aneja et al., 2004; Ukil et al., 2006; Gosslau et al., 2011). Coincidentally, this compound was found to show a strong anti-inflammatory effect by refraining TNF- α -mediated activation of I κ B kinase and

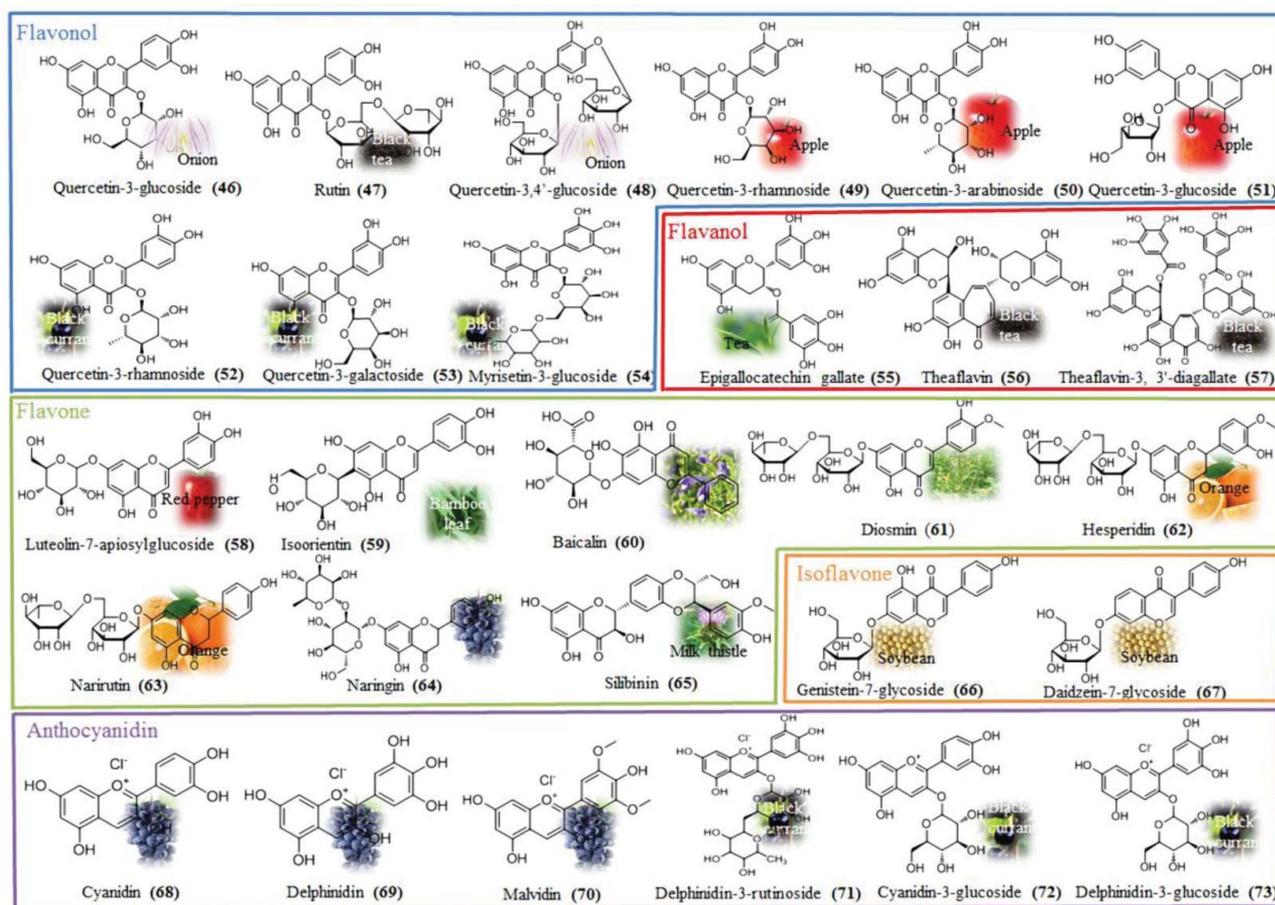


Figure 5. Representative natural glycosylation flavonoid and their dietary sources.

subsequent activation of the $\kappa\text{B-}\alpha/\text{NF-}\kappa\text{B}$ pathway (Aneja et al., 2004). Results of a study by Lin et al. (2005) provided a scientific evidence suggesting that rutinose at C7 is a negative moiety in flavonoid since it inhibited LPS-induced NO production and heme oxygenase-1, reducing LPS-induced iNOS and NO production. Hesperetin (5,7,3'-trihydroxy-4'-methoxyflavanone) and naringenin (5,7,4'-trihydroxy flavanone), and corresponding glycones, hesperidin (compound 62, 5,7,3'-trihydroxy-4'-methoxy-flavanone 7-O-rhamnoglucoside) and naringin (compound 64, 5,7,4'-trihydroxy flavanone 7-O-rhamno glucoside), were used to evaluate the importance of rutinose at C7 for the inhibitory effects of flavonoids on LPS-induced NO production in macrophages. Results showed that rutinose at C7 is critical for the anti-inflammatory activities of flavonoids (Lin et al., 2005).

C-glycosylation

Most of the flavonoid glycosides are O-glycosides; however, sugars can also be bound to a flavonoid moiety through a C-C bond, hence developing C-glycosides (Figure 5). Until now, there is no systematic study available to explain how the location of C-glycosylation influences on the biological activities of flavonoids (Xiao et al., 2016). To investigate the anti-inflammatory effect of C-glycosylation at different positions of a given flavonoid, the structure-activity relationship and a pair of isomeric C-glycosylated derivatives were employed. Yoo et al.

(2014) determined the effects of C-glycosylflavone isomer pairs (orientin, isoorientin, vitexin and isovitexin) on the expression of cellular adhesion molecules (CAMs) in high mobility group box-1 (HMGB1)-stimulated endothelial cells.

Structure-activity relationship revealed the effect of an existence of 3'-OH functional group in the B-ring and a position of C-glucose on the chemical structure of flavone (as discussed in section Hydroxylation) as shown in (Figure 6). Orientin and isoorientin with 3'-OH group showed activities against HMGB1 and its receptors while vitexin and isovitexin without 3'-OH group showed no effect, indicating that the existence of 3'-OH group of flavone plays a pivotal role in anti-inflammatory activities (Yoo et al. 2014). Furthermore, orientin with 8-C-glucoside was more active than isoorientin with 6-C-glucoside in anti-inflammatory activities both *in vitro* and *in vivo* (Choi et al. 2014; Yoo et al. 2014). Orientin, which has been used as an anti-inflammatory herb in China, regulates the key molecules involved in inflammation. For example, orientin (at a tested doses 1–40 μM) suppressed the production of IL-6 and TNF- α in LPS-induced vascular inflammatory response, which is relevant to NF- κB and extracellular signal-regulated kinase (ERK) pathway suppression (Lee et al., 2014). Ku et al. (2014) showed that a high glucose-induced vascular inflammation is attenuated by orientin (5–50 μM) through the regulation of MCP-1, IL-8, reactive oxygen species (ROS) and NF- κB . Liu et al. (2012) investigated inhibitory effects of three flavonoid-C-glycosides

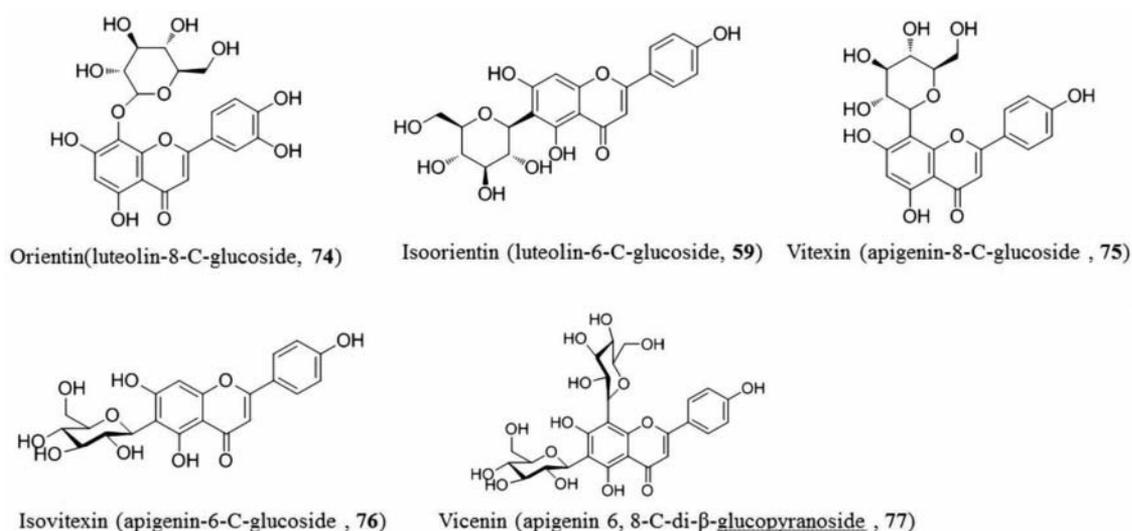


Figure 6. Anti-inflammatory effect of major C-glycosylation flavonoids in dietary foods.

isolated from fenugreek spice on COX-1 and COX-2 enzymes. Among them, the flavone 8-C-glycoside (vitexin) showed the best COX-2 enzyme inhibition as compared to 6-C-glycosides (isovitexin) and 6,8-C-diglycosides (vicenin). However, COX-1 inhibition effect of flavone 6,8-C-diglycosides was better than flavone 6-or 8-C-glycosides (Liu et al. 2012).

Conclusion

Polyphenols show anti-inflammatory effects both *in vitro* and *in vivo*. Several cellular mechanisms are proposed in order to explain their mode of action. No single mechanism can explain all of their activities *in vivo*. The continuous efforts should be made to develop a new insight into the anti-inflammatory effect of phytochemicals, and eventually lead to the development of a new class of anti-inflammatory agents. Dietary intake of flavonoids is suggested to prevent and lower the risk of chronic diseases. In this review, we partially discussed the possible mechanisms by which flavonoids play an important role in the regulation of inflammatory processes. It would be beneficial with a more profound characterization of flavonoid pharmacokinetics and a refinement of structure–activity molecular optimization. Regarding the safety, ability, bioavailability, and the anti-inflammatory effects of flavonoids, they are likely to have a potential role in preventive and therapeutic roles in chronic inflammatory conditions. However, more extensive researches on flavonoids strengthening the network of inflammatory responses are required in the future.

Conflict of interest

None declared

Abbreviations

COX Cyclooxygenase
CXCL Chemokine (C-X-C motif) ligand

ERK Extracellular signal-regulated kinase
ICAM-1 Intercellular adhesion molecule-1
IκB Inhibitor of κB
IKK IκB kinase
IL Interleukin
iNOS Inducible nitric oxide synthase
JAK Janus tyrosine kinase
JNK c-Jun N-terminal kinase
LPS Lipopolysaccharide
LOX Lipoxygenase
MAPK Mitogen-activated protein kinase
NF-κB Nuclear factor-κB
NO Nitric oxide
NOS Nitric oxide synthase
PI3K Phosphatidylinositol 3-kinase
PKC phospho kinase C
PLA2 Phospholipase A2
PGE2 Prostaglandin E2
ROS Reactive oxygen species
STAT Signal transducers and activators of transcription
TNF Tumor necrosis factor
VCAM-1 vascular cell adhesion molecule-1

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References

- Agullo, G., Gamet-Payrastré, L., Manenti, S., Viala, C., Rémésy, C., Chap, H. and Payrastré, B. (1997). Relationship between flavonoid structure and inhibition of phosphatidylinositol 3-kinase: a comparison with tyrosine kinase and protein kinase C inhibition. *Biochem. Pharmacol.* 53:1649–1657.
- Amaral, S., Mira, L., Nogueira, J. M. F., da Silva, A. P. and Florêncio, M. H. (2009). Plant extracts with anti-inflammatory properties—A new approach for characterization of their bioactive compounds and establishment of structure–antioxidant activity relationships. *Bioorganic Med. Chem.* 17:1876–1883.

- Aneja, R., Odoms, K., Denenberg, A. G. and Wong, H. R. (2004). Theaflavin, a black tea extract, is a novel anti-inflammatory compound. *Crit. Care Med.* **32**:2097–2103.
- Benavente-García, O. and Castillo, J. (2008). Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and anti-inflammatory activity. *J. Agric. Food Chem.* **56**:6185–6205.
- Bernini, R., Crisante, F. and Ginnasi, M. C. (2011). A convenient and safe O-methylation of flavonoids with dimethyl carbonate (DMC). *Molecules* **16**:1418–1425.
- Bonfili, L., Cecarini, V., Amici, M., Cuccioloni, M., Angeletti, M., Keller, J. N. and Eleuteri, A. M. (2008). Natural polyphenols as proteasome modulators and their role as anti-cancer compounds. *FEBS J.* **275**:5512–5526.
- Bors, W., Heller, W., Michel, C. and Saran, M. (1990a). Radical chemistry of flavonoid antioxidants. In: *Antioxidants in Therapy and Preventive Medicine*, pp. 165–170. Emerit, I., Ed. Plenum Press, New York.
- Bors, W., Heller, W., Michel, C. and Saran, M. (1990b). Flavonoids as antioxidants: Determination of radical-scavenging efficiencies. *Methods Enzymol.* **186**:343–354.
- Burda, S. and Oleszek, W. (2001). Antioxidant and antiradical activities of flavonoids. *J. Agric. Food Chem.* **49**:2774–2779.
- Byun, S., Lee, K. W., Jung, S. K., Lee, E. J., Hwang, M. K., Lim, S. H. and Dong, Z. (2010). Luteolin inhibits protein kinase C ϵ and c-Src activities and UVB-induced skin cancer. *Cancer Res.* **70**:2415–2423.
- Cao, G., Sofic, E. and Prior, R. L. (1997). Antioxidant and prooxidant behavior of flavonoids: structure-activity relationships. *Free Radical Biol. Med.* **22**:749–760.
- Cao, H., Chen, X. Q., Jassbi, A. R. and Xiao, J. B. (2015). Microbial biotransformation of bioactive flavonoids. *Biotechnol. Adv.* **33**:214–223.
- Cavet, M. E., Harrington, K. L., Vollmer, T. R., Ward, K. W. and Zhang, J. Z. (2011). Anti-inflammatory and anti-oxidative effects of the green tea polyphenol epigallocatechin gallate in human corneal epithelial cells. *Molecul. Vision* **17**:533.
- Chen, C. C., Chow, M. P., Huang, W. C. and Lin, Y. C. and Chang, Y. J. (2004). Flavonoids inhibit tumor necrosis factor- α -induced up-regulation of intercellular adhesion molecule-1 (ICAM-1) in respiratory epithelial cells through activator protein-1 and nuclear factor- κ B: structure-activity relationships. *Mol. Pharmacol.* **66**:683–693.
- Chen, D., Daniel, K. G., Chen, M. S., Kuhn, D. J., Landis-Piowar, K. R. and Dou, Q. P. (2005). Dietary flavonoids as proteasome inhibitors and apoptosis inducers in human leukemia cells. *Biochem. Pharmacol.* **69**:1421–1432.
- Chen, L. and Kang, Y. H. (2013). Anti-inflammatory and antioxidant activities of red pepper (*Capsicum annum* L.) stalk extracts: Comparison of pericarp and placenta extracts. *J. Funct. Foods* **5**:1724–1731.
- Chen, L. and Kang, Y. H. (2014a). Antioxidant and enzyme inhibitory activities of Plebeian Herba (*Salvia plebeia* R. Br.) under different cultivation conditions. *J. Agric. Food Chem.* **62**:2190–2197.
- Chen, L., Kang, Y. H. and Suh, J. K. (2014b). Roasting processed oriental melon (*Cucumis melo* L. var. *makuwa* Makino) seed influenced the triglyceride profile and the inhibitory potential against key enzymes relevant for hyperglycemia. *Food Res. Int.* **56**:236–242.
- Chen, L., Teng, H., Fang, T. and Xiao, J. (2016). Agrimonolide from *Agrimonia pilosa* suppresses inflammatory responses through down-regulation of COX-2/iNOS and inactivation of NF- κ B in lipopolysaccharide-stimulated macrophages. *Phytomedicine.* **23**:846–855. doi:10.1016/j.phymed.2016.03.016.
- Chen, W. P., Wang, Y. L., Tang, J. L., Hu, P. F., Bao, J. P. and Wu, L. D. (2012). Morin inhibits interleukin-1 β -induced nitric oxide and prostaglandin E 2 production in human chondrocytes. *Int. Immunopharmacol.* **12**:447–452.
- Choi, J. S., Choi, Y. J., Park, S. H., Kang, J. S. and Kang, Y. H. (2004). Flavones mitigate tumor necrosis factor- α -induced adhesion molecule upregulation in cultured human endothelial cells: role of nuclear factor- κ B. *J. Nutr.* **134**:1013–1019.
- Choi, J. S., Islam, M. N., Ali, M. Y., Kim, Y. M., Park, H. J., Sohn, H. S. and Jung, H. A. (2014). The effects of C-glycosylation of luteolin on its antioxidant, anti-Alzheimer's disease, anti-diabetic, and anti-inflammatory activities. *Arch. Pharmacol. Res.* **37**:1354–1363.
- Cholbi, M. R., Paya, M. and Alcaraz, M. J. (1991). Inhibitory effect of phenolic compounds on CC14-induced microsomal lipid peroxidation. *Experientia* **47**:195–199.
- Comalada, M., Camuesco, D., Sierra, S., Ballester, I., Xaus, J., Gálvez, J. and Zarzuelo, A. (2005). In vivo quercitrin anti-inflammatory effect involves release of quercetin, which inhibits inflammation through down-regulation of the NF- κ B pathway. *Eur. J. Immunol.* **35**:584–592.
- Crespy, V., Morand, C., Besson, C., Manach, C., Demigne, C. and Remesy, C. (2002). Quercetin, but not its glycosides, is absorbed from the rat stomach. *J. Agric. Food Chem.* **50**:618–621.
- D'Archivio, M., Filesì, C., Di Benedetto, R., Gargiulo, R., Giovannini, C. and Masella, R. (2007). Polyphenols, dietary sources and bioavailability. *Annali Dell'Istituto Superiore di Sanità* **43**:348–361.
- Day, A. J., DuPont, M. S., Ridley, S., Rhodes, M., Rhodes, M. J., Morgan, M. R. and Williamson, G. (1998). Deglycosylation of flavonoid and isoflavonoid glycosides by human small intestine and liver β -glucosidase activity. *FEBS Lett.* **436**:71–75.
- Do, Q. T., Driscoll, M., Slitt, A., Seeram, N., Peppard, T. L. and Bernard, P. (2014). Reverse pharmacognosy: a tool to accelerate the discovery of new bioactive food ingredients. *Food informatics* (111–130). Springer International Publishing eds., Karina Martinez-Mayorga, José Luis Medina-Franco, the location is Universidad Nacional Autónoma de México Instituto de Química, Mexico City, Mexico.
- Elmadfa, I. and Wagner, K. H. (2008). New aspects in quality and biofunctionality of foods. *Ann. Nutr. Metab.* **52**:115–134.
- Ferrandiz, M. L. and Alcaraz, M. J. (1991). Anti-inflammatory activity and inhibition of arachidonic acid metabolism by flavonoids. *Agents Actions* **32**:283–288.
- Folmer, F., Dicato, M. and Diederich, M. (2012). From the deepest sea shelf to the uppermost kitchen cabinet shelf: the quest for novel TNF- α inhibitors. *Curr. Topics Med. Chem.* **12**:1392–1407.
- Galvez, J., Coelho, G., Crespo, M. E., Cruz, T., Rodríguez-Cabezas, M. E., Concha, A. and Zarzuelo, A. (2001). Intestinal anti-inflammatory activity of Morin on chronic experimental colitis in the rat. *Alimentary Pharmacol. Therapeutics* **15**:2027–2039.
- García-Lafuente, A., Guillamón, E., Villares, A., Rostagno, M. A. and Martínez, J. A. (2009). Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. *Inflammat. Res.* **58**:537–552.
- García-Mediavilla, V., Crespo, I., Collado, P. S., Esteller, A., Sánchez-Campos, S., Tuñón, M. J. and González-Gallego, J. (2007). The anti-inflammatory flavones quercetin and kaempferol cause inhibition of inducible nitric oxide synthase, cyclooxygenase-2 and reactive C-protein, and down-regulation of the nuclear factor kappaB pathway in Chang Liver cells. *Eur. J. Pharmacol.* **557**:221–229.
- Gee, J. M., DuPont, M. S., Rhodes, M. J. and Johnson, I. T. (1998). Quercetin glucosides interact with the intestinal glucose transport pathway. *Free Radical Biol. Med.* **25**:19–25.
- Gosslau, A., Jao, E., Li, D., Huang, M. T., Ho, C. T., Evans, D. and Chen, K. Y. (2011). Effects of the black tea polyphenol theaflavin-2 on apoptotic and inflammatory pathways *in vitro* and *in vivo*. *Mol. Nutr. Food Res.* **55**:198–208.
- Graefe, E. U., Wittig, J., Mueller, S., Riethling, A. K., Uehleke, B., Drewelow, B., ... Veit, M. (2001). Pharmacokinetics and bioavailability of quercetin glycosides in humans. *J. Clin. Pharmacol.* **41**:492–499.
- Gregoris, E. and Stevanato, R. (2010). Correlations between polyphenolic composition and antioxidant activity of Venetian propolis. *Food Chem. Toxicol.* **48**:76–82.
- Guerrero, L., Castillo, J., Quiñones, M., García-Vallvé, S., Arola, L., Pujadas, G. and Muguera, B. (2012). Inhibition of angiotensin-converting enzyme activity by flavonoids: structure-activity relationship studies. 10.1371/journal.pone.0049493
- Ha, S. K., Moon, E. and Kim, S. Y. (2010). Chrysin suppresses LPS-stimulated proinflammatory responses by blocking NF- κ B and JNK activations in microglia cells. *Neurosci. Lett.* **485**:143–147.
- Hämäläinen, M., Nieminen, R., Asmawi, M. Z., Vuorela, P., Vapaatalo, H. and Moilanen, E. (2011). Effects of flavonoids on prostaglandin E2 production and on COX-2 and mPGES-1 expressions in activated macrophages. *Planta Medica* **77**:1504–1511.

- Harashtani, O. A., Moin, S., Tham, C. L., Liew, C. Y., Ismail, N., Rajajendram, R., Harith, H. H., Zakaria, Z. A., Mohamad, A. S., Sulaiman, M. R. and Israf, D. A. (2010). Flavonoid combinations cause synergistic inhibition of proinflammatory mediator secretion from lipopolysaccharide-induced RAW 264.7 cells. *Inflammat. Res.* **59**:711–721.
- Heller, W. and Forkmann, G. (1993). Biosynthesis, in *The Flavonoids. Advances in Research Since 1986.* (Harborne JB ed) Chapman & Hall, London; 499–535.
- Hirano, T., Higa, S., Arimitsu, J., Naka, T., Ogata, A., Shima, Y. and Kawai, M. (2006). Luteolin, a flavonoid, inhibits AP-1 activation by basophils. *Biochem. Biophys. Res. Communicat.* **340**:1–7.
- Hirao, K., Yumoto, H., Nakanishi, T., Mukai, K., Takahashi, K., Takegawa, D. and Matsuo, T. (2010). Tea catechins reduce inflammatory reactions via mitogen-activated protein kinase pathways in toll-like receptor 2 ligand-stimulated dental pulp cells. *Life Sci.* **86**:654–660.
- Hollman, P. C., De Vries, J. H., van Leeuwen, S. D., Mengelers, M. J. and Katan, M. B. (1995). Absorption of dietary quercetin glycosides and quercetin in healthy ileostomy volunteers. *Amer. J. Clin. Nutr.* **62**:1276–1282.
- Hollman, P. C. H. and Katan, M. B. (1997). Absorption, metabolism and health effects of dietary flavonoids in man. *Biomed. Pharmacother.* **51**:305–310.
- Hollman, P. C., Katan, M. B., Seiler, P. J., Autrup, L. J. and Autrup, H. (1998). Bioavailability and health effects of dietary flavonols in man. **In: Diversification in Toxicology-Man and Environment**, pp. 237–248. Springer Berlin Heidelberg.
- Hougee, S., Sanders, A., Faber, J., Graus, Y. M., van den Berg, W. B., Garssen, J., ... Hoijer, M. A. (2005). Decreased pro-inflammatory cytokine production by LPS-stimulated PBMC upon *in vitro* incubation with the flavonoids apigenin, luteolin or chrysin, due to selective elimination of monocytes/macrophages. *Biochem. Pharmacol.* **69**:241–248.
- Horia, E. and Watkins, B. A. (2006). Complementary actions of docosahexaenoic acid and genistein on COX-2, PGE2 and invasiveness in MDA-MB-231 breast cancer cells. *Carcinogenesis* **28**:809–815.
- Hutchins, A. M., Slavin, J. L. and Lampe, J. W. (1995). Urinary isoflavonoid phytoestrogen and lignan excretion after consumption of fermented and unfermented soy products. *J. Amer. Dietetic Assoc.* **95**:545–551.
- Jaganath, I. B., Mullen, W., Edwards, C. A. and Crozier, A. (2006). The relative contribution of the small and large intestine to the absorption and metabolism of rutin in man. *Free Radical Res.* **40**:1035–1046.
- Izumi, T., Piskula, M. K., Osawa, S., Obata, A., Tobe, K., Saito, M. and Kikuchi, M. (2000). Soy isoflavone aglycones are absorbed faster and in higher amounts than their glucosides in humans. *J. Nutr.* **130**:1695–1699.
- Jinsart, W., Ternal, B. and Polya, G. M. (1991). Inhibition of wheat embryo calcium-dependent protein kinase and avian myosin light chain kinase by flavonoids and related compounds. *Biol. Chem. Hoppe-Seyler* **372**:819–828.
- Kanazawa, K., Uehara, M., Yanagitani, H. and Hashimoto, T. (2006). Bioavailable flavonoids to suppress the formation of 8-OHdG in HepG2 cells. *Arch. Biochem. Biophys.* **455**:197–203.
- Kiecolt-Glaser, J. K. (2010). Stress, food, and inflammation: psychoneuroimmunology and nutrition at the cutting edge. *Psychosomatic Med.* **72**:365.
- Kim, H. K., Cheon, B. S., Kim, Y. H., Kim, S. Y. and Kim, H. P. (1999b). Effects of naturally occurring flavonoids on nitric oxide production in the macrophage cell line RAW 264.7 and their structure-activity relationships. *Biochem. Pharmacol.* **58**:759–765.
- Kim, S. H., Jun, C. D., Suk, K., Choi, B. J., Lim, H., Park, S. and ... Shin, T. Y. (2006b). Gallic acid inhibits histamine release and pro-inflammatory cytokine production in mast cells. *Toxicol. Sci.* **91**:123–131.
- Kim, B. G., Jung, B. R., Lee, Y., Hur, H. G., Lim, Y. and Ahn, J. H. (2006a). Regiospecific flavonoid 7-O-methylation with *Streptomyces avermitilis* O-methyltransferase expressed in *Escherichia coli*. *J. Agric. Food Chem.* **54**:823–828.
- Kim, D. H., Kim, S. Y., Park, S. Y. and Han, M. J. (1999a). Metabolism of quercitrin by human intestinal bacteria and its relation to some biological activities. *Biol. Pharmaceut. Bull.* **22**:749–751.
- Kim, H. P., Son, K. H., Chang, H. W. and Kang, S. S. (2004). Anti-inflammatory plant flavonoids and cellular action mechanisms. *J. Pharmacol. Sci.* **96**:229–245.
- Kim, J. W., Lee, J. H., Hwang, B. Y., Mun, S. H., Ko, N. Y., Kim, D. K. and Choi, W. S. (2009). Morin inhibits Fyn kinase in mast cells and IgE-mediated type I hypersensitivity response *in vivo*. *Biochem. Pharmacol.* **77**:1506–1512.
- Ku, S. K., Kwak, S. and Bae, J. S. (2014). Orientin inhibits high glucose-induced vascular inflammation *in vitro* and *in vivo*. *Inflammation* **37**:2164–2173.
- Kumazawa, S., Hamasaka, T. and Nakayama, T. (2004). Antioxidant activity of propolis of various geographic origins. *Food Chem.* **84**:329–339.
- Kurowska, E. M. and Manthey, J. A. (2004). Hypolipidemic effects and absorption of citrus polymethoxylated flavones in hamsters with diet-induced hypercholesterolemia. *J. Agric. Food Chem.* **52**:2879–2886.
- Landolfi, R., Mower, R. L. and Steiner, M. (1984). Modification of platelet function and arachidonic acid metabolism by bioflavonoids. *Biochem. Pharmacol.* **33**:1525–1530.
- Lee, C. Y. (2013). Challenges in providing credible scientific evidence of health benefits of dietary polyphenols. *J. Funct. Foods* **5**:524–526.
- Lee, W., Ku, S. K. and Bae, J. S. (2014). Vascular barrier protective effects of orientin and isoorientin in LPS-induced inflammation *in vitro* and *in vivo*. *Vascular Pharmacol.* **62**:3–14.
- Li, R., Huang, Y. G., Fang, D. and Le, W. D. (2004). (–)-Epigallocatechin gallate inhibits lipopolysaccharide-induced microglial activation and protects against inflammation-mediated dopaminergic neuronal injury. *J. Neurosci. Res.* **78**:723–731.
- Liang, Y. C., Huang, Y. T., Tsai, S. H., Lin-Shiau, S. Y., Chen, C. F. and Lin, J. K. (1999). Suppression of inducible cyclooxygenase and inducible nitric oxide synthase by apigenin and related flavonoids in mouse macrophages. *Carcinogenesis* **20**:1945–1952.
- Libby, P. (2007). Inflammatory mechanisms: the molecular basis of inflammation and disease. *Nutr. Rev.* **65**:140–146.
- Lin, H. Y., Shen, S. C. and Chen, Y. C. (2005). Anti-inflammatory effect of heme oxygenase 1: Glycosylation and nitric oxide inhibition in macrophages. *J. Cell. Physiol.* **202**:579–590.
- Liu, Y., Liu, G. M., Cao, M. J., Chen, Q., Sun, L. and Ji, B. (2017). Potential Retinal Benefits of Dietary Polyphenols Based on Their Permeability across the Blood–Retinal Barrier. *J. Agric. Food Chem.* **65**:3179–3189.
- Liu, Y., Kakani, R. and Nair, M. G. (2012). Compounds in functional food fenugreek spice exhibit anti-inflammatory and antioxidant activities. *Food Chem.* **131**:1187–1192.
- Manach, C., Morand, C., Texier, O. and Favier, M. L. (1995). Quercetin metabolites in plasma of rats fed diets containing rutin or quercetin. *J. Nutr.* **125**:1911.
- Mastuda, H., Morikawa, T., Ueda, K., Managi, H. and Yoshikawa, M. (2002). Structural requirements of flavonoids for inhibition of antigen-induced degranulation, TNF- α and IL-4 production from RBL-2H3 cells. *Bioorganic Med. Chem.* **10**:3123–3128.
- Matsuda, H., Morikawa, T., Ando, S., Toguchida, I. and Yoshikawa, M. (2003). Structural requirements of flavonoids for nitric oxide production inhibitory activity and mechanism of action. *Bioorganic Med. Chem. Lett.* **11**:1995–2000.
- Medeiros, K. C. P., Figueiredo, C. A. V., Figueredo, T. B., Freire, K. R. L., Santos, F. A. R., Alcantara-Neves, N. M. and Piuvezam, M. R. (2008). Anti-allergic effect of bee pollen phenolic extract and myricetin in ovalbumin-sensitized mice. *J. Ethnopharmacol.* **119**:41–46.
- Mennen, L. I., Sapinho, D., de Bree, A., Arnault, N., Bertrais, S., Galan, P. and Hercberg, S. (2004). Consumption of foods rich in flavonoids is related to a decreased cardiovascular risk in apparently healthy French women. *J. Nutr.* **134**:923–926.
- Mestas, J. and Ley, K. (2008). Monocyte-endothelial cell interactions in the development of atherosclerosis. *Trends Cardiovascular Med.* **18**:228–232.
- Min, Y. D., Choi, C. H., Bark, H., Son, H. Y., Park, H. H., Lee, S. and Kim, S. H. (2007). Quercetin inhibits expression of inflammatory cytokines through attenuation of NF- κ B and p38 MAPK in HMC-1 human mast cell line. *Inflammat. Res.* **56**:210–215.
- Mothana, R. A., Al-Said, M. S., Al-Rehaily, A. J., Thabet, T. M., Awad, N. A., Lalk, M. and Lindequist, U. (2012). Anti-inflammatory, antinociceptive, antipyretic and antioxidant activities and phenolic

- constituents from *Loranthus regularis* Steud. ex Sprague. *Food Chem.* **130**:344–349.
- Murakami, A., Koshimizu, K., Ohigashi, H., Kuwahara, S., Kuki, W., Takahashi, Y. and Matsuoka, Y. (2002). Characteristic rat tissue accumulation of nobiletin, a chemopreventive polymethoxy flavonoid, in comparison with luteolin. *Biofactors* **16**:73–82.
- Nakahata, N., Kutsuwa, M., Kyo, R., Kubo, M., Hayashi, K. and Ohizumi, Y. (1998). Analysis of inhibitory effects of scutellariae radix and baicalin on prostaglandin E2 production in rat C6 glioma cells. *Amer. J. Chinese Med.* **26**:311–323.
- Nomura, M., Takahashi, T., Nagata, N., Tsutsumi, K., Kobayashi, S., Akiba, T. and Miyamoto, K. I. (2008). Inhibitory mechanisms of flavonoids on insulin-stimulated glucose uptake in MC3T3-G2PA6 adipose cells. *Biol. Pharmaceut. Bull.* **31**:1403–1409.
- Pan, M. H., Lai, C. S., Dushenkov, S. and Ho, C. T. (2009). Modulation of inflammatory genes by natural dietary bioactive compounds. *J. Agric. Food Chem.* **57**:4467–4477.
- Pelzer, L. E., Guardia, T., Juarez, A. O. and Guerreiro, E. (1998). Acute and chronic antiinflammatory effects of plant flavonoids. *Il Farmaco* **53**:421–424.
- Pérez-Jiménez, J., Neveu, V., Vos, F. and Scalbert, A. (2010). Systematic analysis of the content of 502 polyphenols in 452 foods and beverages: an application of the phenol-explorer database. *J. Agric. Food Chem.* **58**:4959–4969.
- Piparo, E. L., Scheib, H., Frei, N., Williamson, G., Grigorov, M. and Chou, C. J. (2008). Flavonoids for controlling starch digestion: Structural requirements for inhibiting human α -amylase. *J. Med. Chem.* **51**:3555–3561.
- Piscoya, J., Rodriguez, Z., Bustamante, S. A., Okuhama, N. N., Miller, M. J. S. and Sandoval, M. (2001). Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: mechanisms of action of the species *Uncaria guianensis*. *Inflammat. Res.* **50**:442–448.
- Plochmann, K., Korte, G., Koutsilieris, E., Richling, E., Riederer, P., Rethwilm, A. and Scheller, C. (2007). Structure–activity relationships of flavonoid-induced cytotoxicity on human leukemia cells. *Arch. Biochem. Biophys.* **460**:1–9.
- Ratty, A. K. and Das, N. P. (1988). Effects of flavonoids on nonenzymatic lipid peroxidation: structure-activity relationship. *Biochem. Med. Metabolic Biol.* **39**:69–79.
- Rhodes, M. J. and Price, K. R. (1996). Analytical problems in the study of flavonoid compounds in onions. *Food Chem.* **57**:113–117.
- Rigobello, M. P., Stevanato, R., Momo, F., Fabris, S., Scutari, G., Boscolo, R., Folda, A. and Bindoli, A. (2004). Evaluation of the antioxidant properties of propofol and its nitrosoderivative. Comparison with homologue substituted phenols. *Free Radical Res.* **38**:315–321.
- Robak, J. and Gryglewski, R. J. (1987). Flavonoids are scavengers of superoxide anions. *Biochem. Pharmacol.* **36**:317–322.
- Rogério, A. P., Kanashiro, A., Fontanari, C., Da Silva, E. V. G., Lucisano-Valim, Y. M., Soares, E. G. and Faccioli, L. H. (2007). Anti-inflammatory activity of quercetin and isoquercitrin in experimental murine allergic asthma. *Inflammat. Res.* **56**:402–408.
- Saadawi, S., Jalil, J., Jasamai, M. and Jantan, I. (2012). Inhibitory effects of acetylmelodorinol, chrysin and polycarpol from *mitrella kentii* on prostaglandin E2 and thromboxane B2 production and platelet activating factor receptor binding. *Molecules* **17**:4824–4835.
- Sae-Wong, C., Matsuda, H., Tewtrakul, S., Tansakul, P., Nakamura, S., Nomura, Y. and Yoshikawa, M. (2011). Suppressive effects of methoxyflavonoids isolated from *Kaempferia parviflora* on inducible nitric oxide synthase (iNOS) expression in RAW 264.7 cells. *J. Ethnopharmacol.* **136**:488–495.
- Sakata, K., Hirose, Y., Qiao, Z., Tanaka, T. and Mori, H. (2003). Inhibition of inducible isoforms of cyclooxygenase and nitric oxide synthase by flavonoid hesperidin in mouse macrophage cell line. *Cancer Lett.* **199**:139–145.
- Sandoval, M., Okuhama, N. N., Zhang, X. J., Condezo, L. A., Lao, J., Angeles, F. M. and Miller, M. J. S. (2002). Anti-inflammatory and antioxidant activities of cat's claw (*Uncaria tomentosa* and *Uncaria guianensis*) are independent of their alkaloid content. *Phytomedicine* **9**:325–337.
- Setchell, K. D., Brown, N. M., Desai, P., Zimmer-Nechemias, L., Wolfe, B. E., Brashear, W. T. and Heubi, J. E. (2001). Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. *J. Nutr.* **131**:1362S–1375S.
- Shanmugam, K., Holmquist, L., Steele, M., Stuchbury, G., Berbaum, K., Schulz, O. and Dobson, G. (2008). Plant-derived polyphenols attenuate lipopolysaccharide-induced nitric oxide and tumour necrosis factor production in murine microglia and macrophages. *Mol. Nutr. Food Res.* **52**:427–438.
- Shen, S. C., Lee, W. R., Lin, H. Y., Huang, H. C., Ko, C. H., Yang, L. L. and Chen, Y. C. (2002). *In vitro* and *in vivo* inhibitory activities of rutin, wogonin, and quercetin on lipopolysaccharide-induced nitric oxide and prostaglandin E 2 production. *Eur. J. Pharmacol.* **446**:187–194.
- Shichijo, M., Yamamoto, N., Tsujishita, H., Kimata, M., Nagai, H. and Kokubo, T. (2003). Inhibition of syk activity and degranulation of human mast cells by flavonoids. *Biol. Pharmaceut. Bull.* **26**:1685–1690.
- Shie, J. J., Chen, C. A., Lin, C. C., Ku, A. F., Cheng, T. J. R., Fang, J. M. and Wong, C. H. (2010). Regioselective synthesis of di-C-glycosylflavones possessing anti-inflammation activities. *Organic Biomol. Chem.* **8**:4451–4462.
- Siess, M. H., Leclerc, J., Canivenclavier, M. C., Rat, P. and Suschetet, M. (1995). Heterogenous effects of natural flavonoids on monooxygenase activities in human and rat liver microsomes. *Toxicol. Appl. Pharmacol.* **130**:73–78.
- Sobocanec, S., Sverko, V., Balog, T., Saric, A., Rusak, G., Likic, S., Kusic, B., Katalinic, V., Radic, S. and Marotti, T. (2006). Oxidant-antioxidant properties of Croatian native propolis. *J. Agric. Food Chem.* **54**:8018–8026.
- Soobrattee, M. A., Neergheen, V. S., Luximon-Ramma, A., Aruoma, O. I. and Bahorun, T. (2005). Phenolics as potential antioxidant therapeutic agents: mechanism and actions. *Mutat. Res.Fundamental Mol. Mechan. Mutagenesis* **579**:200–213.
- Stalmach, A., Mullen, W., Steiling, H., Williamson, G., Lean, M. E. J. and Crozier, A. (2010). Absorption, metabolism, and excretion of green tea flavan-3-ols in humans with an ileostomy. *Mol. Nutr. Food Res.* **54**:323–334.
- Suh, Y., Afaq, F., Johnson, J. J. and Mukhtar, H. (2009). A plant flavonoid fisetin induces apoptosis in colon cancer cells by inhibition of COX2 and Wnt/EGFRNF- κ B-signaling pathways. *Carcinogenesis* **30**:300–307.
- Sung, M. S., Lee, E. G., Jeon, H. S., Chae, H. J., Park, S. J., Lee, Y. C. and Yoo, W. H. (2012). Quercetin inhibits IL-1 β -induced proliferation and production of MMPs, COX-2, and PGE2 by rheumatoid synovial fibroblast. *Inflammation* **35**:1585–1594.
- Suou, K., Taniguchi, F., Tagashira, Y., Kiyama, T., Terakawa, N. and Harada, T. (2011). Apigenin inhibits tumor necrosis factor α -induced cell proliferation and prostaglandin E2 synthesis by inactivating NF κ B in endometriotic stromal cells. *Fertility Sterility* **95**:1518–1521.
- Suzuki, J. I., Ogawa, M., Futamatsu, H., Kosuge, H., Sagesaka, Y. M. and Isobe, M. (2007). Tea catechins improve left ventricular dysfunction, suppress myocardial inflammation and fibrosis, and alter cytokine expression in rat autoimmune myocarditis. *Eur. J. Heart Failure* **9**:152–159.
- Ta, N. and Walle, T. (2007). Aromatase inhibition by bioavailable methylated flavones. *J. Steroid Biochem. Mol. Biol.* **107**:127–129.
- Tadera, K., Minami, Y., Takamatsu, K. and Matsuoka, T. (2006). Inhibition of ALPHA-Glucosidase and ALPHA-Amylase by Flavonoids. *J. Nutr. Sci. Vitaminol.* **52**:149–153.
- Takano-Ishikawa, Y., Goto, M. and Yamaki, K. (2006). Structure-activity relations of inhibitory effects of various flavonoids on lipopolysaccharide-induced prostaglandin E 2 production in rat peritoneal macrophages: Comparison between subclasses of flavonoids. *Phytomedicine* **13**:310–317.
- Teng, H., Chen, L. and Song, H. (2016). The potential beneficial effects of phenolic compounds isolated from *A. pilosa* Ledeb on insulin-resistant hepatic HepG2 cells. *Food Funct.* **7**:4400–4409.
- Tewtrakul, S., Subhadhirasakul, S., Karalai, C., Ponglimanont, C. and Cheenpracha, S. (2009). Anti-inflammatory effects of compounds from *Kaempferia parviflora* and *Boesenbergia pandurata*. *Food Chem.* **115**:534–538.
- Tjendraputra, E., Tran, V. H., Liu-Brennan, D., Roufogalis, B. D. and Duke, C. C. (2001). Effect of ginger constituents and synthetic

- analogues on cyclooxygenase-2 enzyme in intact cells. *Bioorganic Chem.* **29**:156–163.
- Ueda, H., Yamazaki, C. and Yamazaki, M. (2004). A hydroxyl group of flavonoids affects oral anti-inflammatory activity and inhibition of systemic tumor necrosis factor- α production. *Biosci., Biotechnol., Biochem.* **68**:119–125.
- Ukil, A., Maity, S. and Das, P. K. (2006). Protection from experimental colitis by theaflavin-3, 3'-digallate correlates with inhibition of IKK and NF- κ B activation. *British J. Pharmacol.* **149**:121–131.
- van Meeteren, M. E., Hendriks, J. J., Dijkstra, C. D. and van Tol, E. A. (2004). Dietary compounds prevent oxidative damage and nitric oxide production by cells involved in demyelinating disease. *Biochem. Pharmacol.* **67**:967–975.
- Walle, T., Ta, N., Kawamori, T., Wen, X., Tsuji, P. A. and Walle, U. K. (2007). Cancer chemopreventive properties of orally bioavailable flavonoids-methylated versus unmethylated flavones. *Biochem. Pharmacol.* **73**:1288–1296.
- Walle, U. K., Galijatovic, A. and Walle, T. (1999). Transport of the flavonoid chrysin and its conjugated metabolites by the human intestinal cell line Caco-2. *Biochem. Pharmacol.* **58**:431–438.
- Wang, S. J., Tong, Y., Lu, S., Yang, R., Liao, X., Xu, Y. F. and Li, X. (2010). Anti-inflammatory activity of myricetin isolated from *Myrica rubra* Sieb. et Zucc. leaves. *Planta Medica* **76**:1492–1496.
- Wang, X. G., Chen, G. Y. and Chen, M. P. (2007). Effect of luteolin on COX-2 and mPGES-1 expression in LPS-induced RAW264. 7 cells. *Zhong yao cai Zhongyaocai. Journal of Chinese Medicinal Materials* **30**:1263–1266.
- Weidmann, A. E. (2012). Dihydroquercetin: More than just an impurity? *Eur. J. Pharmacol.* **684**:19–26.
- Wen, X. and Walle, T. (2006). Methylated flavonoids have greatly improved intestinal absorption and metabolic stability. *Drug Metabol. Disposit.* **34**:1786–1792.
- Wu, W. M., Lu, L., Long, Y., Wang, T., Liu, L., Chen, Q. and Wang, R. (2007). Free radical scavenging and antioxidative activity of caffeic acid phenethyl ester (CAPE) and its related compounds in solution and membranes: a structure–activity insight. *Food Chemistry* **105**:107–115.
- Xia, J., Gao, J., Inagaki, Y., Kokudo, N., Nakata, M. and Tang, W. (2013). Flavonoids as potential anti-hepatocellular carcinoma agents: recent approaches using HepG2 cell line. *Drug Disc. Therap.* **7**:1–8.
- Xiao, J. B., Kai, G. Y., Yamamoto, K. and Chen, X. Q. (2013a). Advance in dietary polyphenols as α -glucosidases inhibitors: a review on structure-activity relationship aspect. *Crit. Rev. Food Sci. Nutr.* **53**:818–836.
- Xiao, J. B., Ni, X. L., Kai, G. Y. and Chen, X. Q. (2013b). A review on structure-activity relationship of dietary polyphenols inhibiting α -amylase. *Crit. Rev. Food Sci. Nutr.* **53**:497–506.
- Xiao, J. B., Ni, X. L., Kai, G. Y. and Chen, X. Q. (2015a). Advance in dietary polyphenols as aldose reductases inhibitors: Structure-activity relationship aspect. *Crit. Rev. Food Sci. Nutr.* **55**:16–31.
- Xiao, J. B. and Högger, P. (2015b). Dietary polyphenols and type 2 diabetes: current insights and future perspectives. *Curr. Med. Chem.* **22**:23–38.
- Xiao, J. B. (2016). Dietary flavonoid aglycones and their glycosides: What show better biological benefits? *Crit. Rev. Food Sci. Nutr.* **9**:1874–1905. DOI: 10.1080/10408398.2015.1032400.
- Xiao, J. B., Capanoglu, E., Jassbi, A. R. and Miron, A. (2016). Advance on the flavonoid C-glycosides and health benefits. *Crit. Rev. Food Sci. Nutr.* **56**:29–45. Doi:10.1080/10408398.2015.1067595.
- Xu, W., Shao, R. and Xiao, J. B. (2016). Is there consistency between the binding affinity and inhibitory potential of natural polyphenols as α -amylase inhibitors? *Crit. Rev. Food Sci. Nutr.* **56**:1630–1639. DOI:10.1080/10408398.2013.793652.
- Yoo, H., Ku, S. K., Lee, T. and Bae, J. S. (2014). Orientin inhibits HMGB1-induced inflammatory responses in HUVECs and in murine polymicrobial sepsis. *Inflammation* **37**:1705–1717.
- Yoon, H. Y., Lee, E. G., Lee, H., Cho, I. J., Choi, Y. J., Sung, M. S. and Yoo, W. H. (2013). Kaempferol inhibits IL-1 β -induced proliferation of rheumatoid arthritis synovial fibroblasts and the production of COX-2, PGE2 and MMPs. *Int. J. Mol. Med.* **32**:971–977.
- You, K. M., Jong, H. G. and Kim, H. P. (1999). Inhibition of cyclooxygenase-lipoxygenase from human platelets by polyhydroxylatedmethoxylated flavonoids isolated from medicinal plants. *Arch. Pharm. Res.* **22**:18–24.
- Zamora-Ros, R., Touillaud, M., Rothwell, J. A., Romieu, I. and Scalbert, A. (2014). Measuring exposure to the polyphenol metabolome in observational epidemiologic studies: current tools and applications and their limits. *Amer. J. Clin. Nutr.* doi: 10.3945/ajcn.113.077743.
- Zamora-Ros, R., Knaze, V., Rothwell, J. A., Hémon, B., Moskal, A., Overvad, K. and Touillaud, M. (2016). Dietary polyphenol intake in Europe: the European Prospective Investigation into Cancer and Nutrition (EPIC) study. *Eur. J. Nutr.* **55**:1359–1375.
- Zhong, Y., Chiou, Y. S., Pan, M. H. and Shahidi, F. (2012). Anti-inflammatory activity of lipophilic epigallocatechin gallate (EGCG) derivatives in LPS-stimulated murine macrophages. *Food Chem.* **134**:742–748.