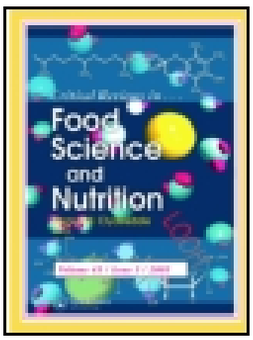


Taylor & Francis
Taylor & Francis Group

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

Intracellular signaling pathways of inflammation modulated by dietary flavonoids: The most recent evidence

Lei Chen, Hui Teng, Zhen Jia, Maurizio Battino , Anca Miron, Zhiling Yu, Hui Cao & Jianbo Xiao

To cite this article: Lei Chen, Hui Teng, Zhen Jia, Maurizio Battino , Anca Miron, Zhiling Yu, Hui Cao & Jianbo Xiao (2017): Intracellular signaling pathways of inflammation modulated by dietary flavonoids: The most recent evidence, Critical Reviews in Food Science and Nutrition, DOI: 10.1080/10408398.2017.1345853

To link to this article: http://dx.doi.org/10.1080/10408398.2017.1345853

Accepted author version posted online: 06 Jul 2017.

Intracellular signaling pathways of inflammation modulated by dietary flavonoids: the most recent evidence

Lei Chen[#,1], Hui Teng[#,1], Zhen Jia[1], Maurizio Battino[2], Anca Miron[3], Zhiling Yu[4,*], Hui Cao[1,5], Jianbo Xiao[5,*]

[1]College of Food Science, Fujian Agriculture and Forestry University, Fuzhou, Fujian 350002, China

[2]Center for Nutrition & Health, Universidad Europea del Atlantico, Santander, Spain and Dept. of Clinical Sciences, Universitr Nutrition & Health, Universidad Europea

[3]Faculty of Pharmacy, Grigore T. Popa University of Medicine and Pharmacy Iasi, Romania

[4]Centre for Cancer and Inflammation Research, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong

[5]Institute of Chinese Medical Sciences, State Key Laboratory of Quality Research in Chinese Medicine, University of Macau, Avenida da Universidade, Taipa, Macau

#Authors contributed equally to this work

*Corresponding author: Jianbo Xiao, Institute of Chinese Medical Sciences, State Key Laboratory of Quality Research in Chinese Medicine, University of Macau, Taipa, Macau. E-mail: jianboxiao@yahoo.com; jianboxiao@umac.mo; Tel: +853-88228522; Mobile:+853-65718163

Zhiling Yu, Centre for Cancer and Inflammation Research, School of Chinese Medicine, Hong Kong Baptist University, Hong Kong. Email: zlyu@hkbu.edu.hk; Tel: +852 3411 2465; Fax: +852 3411 2461

Abstract

Background

Dietary flavonoids, which occur in many plant foods, are considered as the most active constituents among the plant-derived ones *in vitro* and *in vivo*. To date, many studies have

addressed the anti-inflammatory activity of flavonoids. However, their considerable structural diversity and *in vivo* bioavailability make them able to modulate different signaling pathways.

Scope and Approach

The present review attempted to summarize and highlight a broad range of inflammation-associated signaling pathways modulated by flavonoids. Finally, based on the current scientist's literature, structure-activity relationships were concluded. hain.

Key Findings and Conclusions

Dietary flavonoids have the ability to attenuate inflammation by targeting different intracellular signaling pathways triggered by NF-κB, AP-1, PPAR, Nrf2, and MAPKs. Identification of the main structural features required for the modulation of these inflammation-related pathways (hydroxylation pattern, C2 = C3 double bond) have an important role to play in the development of new anti-inflammatory drugs.

Keywords

flavonoids, inflammation, intracellular signaling pathways, structure-activity relationship

Introduction

Flavonoids are polyphenolic compounds with a phenylbenzopyran structure which are widely distributed in plants. Depending on the level of oxidation and substitution pattern of the C-ring, flavonoids can be divided in several classes such as flavones, flavonols, flavanones, flavanonols, flavan-3-ols, anthocyanidins, and isoflavones (Pereira et al., 2009; Kumar and Pandey, 2013; Marín et al., 2015). Chalcones, having an open C-ring, are also a class of flavonoids (Ferreyra et al., 2012) (Figure 1). Hydroxyl group substitution often occurs at C-3, -5, -7, -2, -3', -4', and -5'. Hydroxyl groups (especially those bound to C-3 and C-7) might be glycosylated with glucose, galactose, rhamnose, arabinose, and glucorhamnose; methylation or acetylation might also occur (Xiao 2017; Xiao et al., 2016). Flavonoids are synthetized by the phenylpropanoid pathway which involves, as an initial step, the conversion of phenylalanine to 4-coumaroyl-CoA. Chalcone synthase and chalcone isomerase are responsible for further generation of chalcones and flavanones, respectively. Other types of flavonoids derive from flavanones by enzyme-catalyzed reactions (Kumar and Pandey, 2013; Marín et al., 2015) (Figure 2).

Flavonoids are very common dietary phytochemicals; they are found abundantly in fruits, vegetables, green and black teas, red wine, cocoa, and cocoa-based products (Kumar and Pandey, 2013; Marín et al., 2015). Most dietary flavonoids (flavones, flavonols, flavanones, anthocyanidins, isoflavones) are glycosides (Erlund, 2004). After ingestion, flavonoid glycosides are enzymatically hydrolysed to aglycones which are further absorbed in the small intestine. Once absorbed, the aglycones are partially metabolized to methylated, glucuronidated, and sulfated conjugates (phase II metabolic reactions). Free aglycones and their conjugates are transported by the portal vein to the liver where they undergo more phase II metabolism. The liver conjugates circulate in the bloodstream and are eliminated in the urine or bile (Xiao and Högger, 2014; Fernandes et al., 2015; Marín et al., 2015).

Flavanols occur as monomers (aglycones and their gallate esters), oligomers and polymers (Erlund, 2004). Similarly to flavonoid aglycones, flavanol monomers (i.e. catechin, epicatechin) undergo extensive phase II metabolic reactions in the gut and liver. Dimers to tetramers are poorly metabolized and absorbed. Flavanols higher than tetramers are not absorbed in the small

intestine (Ou and Gu, 2014). However, barely 5 to 10% of total flavonoids may be absorbed in the small intestine and undergo subsequent metabolism. Unabsorbed flavonoids reach the colon and are further excreted in the faeces (Gleichenhagen and Schieber, 2016).

Flavonoids have been reported to possess a wide variety of biological activities such as antioxidant activity, anti-inflammatory activity, hepatoprotective effect, antibacterial activity, antiviral activity, anticancer activity, and antidiabetic activity (Benavente-Garcia and Castillo, 2008; Kumar and Pandey, 2013; Xiao and Högger, 2015; Loizzo et al., 2016). Currently, flavonoids are used as functional ingredients in dietary and health food supplements and cosmetics. Various experimental methods have been employed to investigate the biological effects of different flavonoids and their safety when used in human therapy (Cao et al., 2015; Xiao et al., 2014; George et al., 2016; Menezes et al., 2016; Luca et al., 2016; Rozmer & Perjesi, 2016). Furthermore, the association between flavonoids and other food constituents, such as carbohydrates, proteins, fatty acids, and minerals, has been inspected since these food constituents might influence the bioaccessibility of flavonoids during digestion, absorption and metabolism in the human body (Gleichenhagen and Schieber, 2016).

This review focuses on dietary flavonoids that modulate inflammation-associated signaling pathways thus regulating the expression of pro-inflammatory mediators. Relationships between the structure of flavonoids and their anti-inflammatory activity are highlighted as well, hoping to offer useful information for the development of new natural source-based anti-inflammatory drugs.

2. Inflammation-associated intracellular signaling pathways

Inflammation is a normal biological response of the organism to physical, chemical or biological stimuli (Karcher and Laufer, 2009). But in some pathological conditions, chronic inflammation can also lead to diseases, such as rheumatoid arthritis, hay fever, atherosclerosis, glomerulonephritis, and gastroenteritis, and sometimes even promotes the progression of cancer. Cytokines (IL-1, IL-6, IL-8, TNF-α, NO, platelet-activating factor, thromboxanes, histamine, C5a and C3a components of the complement system) can significantly promote the progression of inflammation (Voronov et al., 1999). Secretion of inflammatory mediators causes increased

vascular permeability, vasodilation, and slow blood flow rate, finally leading to the recruitment and extravasation of leukocytes. Leukocytes, especially granulocytes, secrete cytokines (TNF-α, IL-6, IL-1) that promote the secretion of other inflammatory mediators and recruite the macrophages to the inflammation site, thus enhancing the inflammatory process.

2.1. Nuclear factor (NF)- κB

Intracellular signaling pathways for the regulation of inflammatory and immune responses in lipopolysaccharide (LPS)-stimulated macrophages involve nuclear transcription factor kappa-B (NF-κB), Janus kinase-signal transducers, and activators of transcription (JAK-STATs), and mitogen-activated protein kinases (MAPKs) (Figure 3) (Clarke et al., 2009). NF-κB is a crucial factor for the regulation of both innate and adaptive immunities, controlling various genes expression when inflammatory responses occur (Li and Verma, 2002). NF-κB family includes NF-κB1 (p50/p105), NF-κB2 (p52/p100), p65 (RelA), RelB, and c-Rel (Oeckinghaus and Ghosh, 2009). Most members of this family (RelB being one exception) homodimerize, as well as form heterodimers with each other. The most prevalent activated form of NF-κB is a heterodimer consisting of p50, p52, and p65 subunits, which contains transactivation domains necessary for gene induction. Production of certain cytokines (TNF-α, IL-6, and IL-8) as well as the expression of cyclooxygenase 2 (COX-2) are mediated by NF-κB. In RAW 264.7 cell models, NF-κB is found to be sequestered in the cytosol as a latent form bound to inhibitory proteins. A set of inhibitors are phosphorylated after LPS stimulation (Chen et al., 2013; Chen et al., 2016a, b). Besides IκB phosphorylation, pro-inflammatory cytokines (TNF- o, IL-6, IL-1a) are also involved in NF-κB activation (Harikumar et al., 2010).

2.2. Nuclear-related factor 2 (Nrf2)

Antioxidant responsive element (ARE) is a *cis*-acting regulatory element of genes encoding phase II detoxification and antioxidant enzymes such as NAD(P)H:quinone oxidoreductase 1 (NQO1), glutathione S-transferases (GSTs), and glutamate-cysteine ligase (Figure 3). Interestingly, it has been reported that Nrf2 (nuclear factor-erythroid 2-related factor-2) regulates a wide array of ARE-driven genes in various cell types (Jung and Kwak, 2010). Under quiescent conditions, the transcription factor Nrf2 interacts with the actin-anchored protein Keap1 that is

mostly localized in the cytoplasm (Kensler et al., 2007). However, it is worthy to note that, as a response to oxidative stress, cysteine sensors within Keap1 are oxidized or conjugated, leading to the accumulation of closed conformation of the Keap1-Nrf2 complex (Dinkova-Kostova et al., 2005). Interaction of Keap1 with Nrf2 triggers the sequestration of Nrf2 in the cytoplasm and enhancement of Nrf2 degradation by proteasomes, conferring a tight regulation of the response (Itoh et al., 2004). Even under oxidative stress conditions when Nrf2 is protected from Keap1 repression, Nrf2 is still showing proteasomal degradation, suggesting that Keap1-independent degradation of the Nrf2 might exist. On the other hand, the prototype coenzymes, such as NAD(P)H-quinone oxidoreductase 1 (NQO1) and glutathione S-transferases (GSTs), and a subset of antioxidant genes including the subunits of γ-glutamylcysteine synthetase (γ-GCS), heme oxygenase 1 (HO-1), and thioredoxin are regulated by the Nrf2-ARE signaling pathway (Talalay and Fahey, 2001; Kawakita et al., 2003). Intracellular reactive oxygen species (ROS) have a fundamental role in the pro-inflammatory responses through the activation of redox-sensitive transcription factors such as NF-κB and activator protein-1 (AP-1), and their up-regulating kinases including MAPKs (p38, ERK and JNK) and PI3K (Kim et al., 2011). Since Nrf2--ARE-regulated genes contribute to the cellular protection against oxidative stress and potentiation of antioxidant defense capacity in cells, modulation of Nrf2--ARE signaling may have profound effects on the redox-sensitive inflammation-regulating factors, such as NF-κB and AP-1. Several pro-inflammatory cytokines including TNF-α, IL-1β, IL-2, IL-6, and IL-12 are overproduced when redox-sensitive NF-κB is activated by ROS. Compounds activating Nrf2 signaling pathway could down-regulate the overproduction of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α (Kim et al., 2011). As ROS trigger NF-κB and AP-1 activation, flavonoids are supposed to attenuate inflammation by reducing the intracellular level of ROS. It is unlikely that flavonoids inactivate ROS by direct scavenging. Although many dietary flavonoids proved to be potent antioxidant agents in *in vitro* models, a similar antioxidant activity is less likely to occur *in vivo*. As already mentioned, after ingestion, dietary flavonoids undergo extensive biotransformation in the small intestine and liver (deglycosylation, oxidation, conjugation, methylation) but also in the large intestine (ring cleavage, reduction of double bonds, decarboxylation). Therefore, little of the parent flavonoid can be detected in plasma

following ingestion; flavonoid metabolites are predominant in systemic circulation and tissues. Flavonoid metabolites have a lower antioxidant capacity than the parent molecules and, in addition, some of them (metabolites having free catechol moiety and/or free hydroxyl group at C-3 position) showed prooxidant effects (increase in the production of hydrogen peroxide and superoxide anion radical). However, prooxidant activity might be beneficial as it causes an increase in detoxifying enzymes and antioxidant defense systems (Procházková et al., 2011).

2.3. Peroxisome proliferator-activated receptors (PPARs)

The peroxisome proliferator-activated receptors **(**PPARs) pertain to a family of nuclear hormone receptors producing their effects through the regulation of transcription of some genes. One of the most interesting aspects on the PPARs is that they seem to integrate inflammation and energy metabolism. Three isoforms of PPARs (α, β-also called δ, and γ) were identified in humans. Numerous studies reported the association between PPAR-α and transcription factors in mediating the inflammatory signaling pathways, including the signal transducer and activator of transcription proteins (STAT), AP-1 complex composed of c-Jun proteins, p50, and p65 proteins (Vona-Davis, et al., 2004). PPAR-γ modulation is very promising for the control of the inflammatory processes. According to a recent study (Celinski et al., 2012), some of PPAR-γ ligands showed a high potential for the therapy of inflammatory bowel diseases. Besides, several anti-inflammatory effects (inhibition of TNF-α, IL-6 and IL-1β production) of PPARs-γ agonists (glitazones) have been described (Jiang et al., 1998; Ricote et al., 1999). Chiba et al. (2001) also reported that PPARs-γ agonists inhibited the production of TNF-α induced by oxidized LDL.

2.4. Mitogen-activated protein kinases (MAPKs)

Different types of pro-inflammatory stimulators, such as LPS or cytokines, can bind to Toll-IL-1 and TNF receptors in macrophages, resulting in the activation of particular signaling transduction profiles which are responsible for the production of inflammatory mediators. MAPK pathway plays an important role in the inflammation. Three major groups of distinctly regulated MAPKs are known in humans that lead to altered gene expressions: extracellular signal-regulated kinase (ERK1/2), JNK, and p38 MAPK. The ERK1/2 pathway, activated by MAP kinase (MKK1 and MKK2), is most commonly linked to cell differentiation and survival,

whereas JNK and p38 MAPK pathways are usually referred to as stress-stimulated MAPKs (Pearson et al., 2001). Once being activated, phosphorylation of MAPKs and activation of several transcription factors including NF-κB, PPAR, and Nrf2 induce the expression of target genes and inflammatory mediators (Owuor and Kong, 2002; Broom et al., 2009). Different MAPKs have multiple substrate specificities; in other words, the interaction of multiple MAPKs cascades is of great importance to integrate the responses and activate distinct sets of genes. Hence, the inhibition of MAPKs could lead to anti-inflammatory effects through modulating the levels of pro- and anti-inflammatory mediators (Kaminska, 2005).

3. Methodology

This study is a literature descriptive review. The data sources we have used were several national (CNKI, Sciinfo, and Wanfang data), and international databases (Sciencedirect, Pubmed, Springer, and Scopus). The main inclusion criteria were the keywords (*anti-inflammatory effect*, *extract*, *flavonoids* and *phenolics*), publishing language (English and Chinese), publication time (2000-2016), and type of study (only clinical trials and experimental researches).

Overall, 632 articles were collected in the first step. Almost 80% were excluded on the basis of the following criteria: lack of relation with the topic according to title and abstract evaluations, incomplete data, congress, and conference proceedings. Finally, 126 studies met the selection criteria and were included in our study (Figure 4).

4. Flavonoids as modulators of inflammatory signaling pathways

A large number of studies have reported on the anti-inflammatory potential of flavonoids, attributing their capacity to attenuate inflammation not only to the antioxidant effects, but also to the ability to modulate several intracellular signaling pathways such as NF-κB, JAK-STATs, and MAPKs (Fig. 5). Dietary flavonoids investigated on their anti-inflammatory potential between 2011 and 2015 and their effects on inflammation-associated intracellular signaling pathways are presented in Fig. 6 and Table 1, respectively.

4.1 Flavones and flavonols

Apigenin, luteolin, and chrysoeriol are well-known flavones which are effective anti-inflammatory agents. These compounds target various molecules in cellular pathways, resulting in reduction of TNF-α secretion and inhibition of NF-κB, p38 MAPK, IL-6, and IL-1β production (Hostetler et al., 2012). By suppression of p65 phosphorylation, these flavones down-regulate TNF-α and iNOS Inos by inactivating NF-κB and interfering MAPK pathway. Particularly, inhibition of p38, ERK, and casein kinase 2 (CK2) activation are reported to be associated with the reduction in TNF-α release from macrophages (Xagorari et al., 2002). Interestingly, luteolin, an inhibitor of CK2, not only showed a beneficial effect on IL-1β *in vitro*, but also promoted NF-κB dependent protective molecules in enterocytes *in vivo*. RAW264.7 cells, after stimulation with LPS and addition of apigenin, luteolin, or diosmetin, showed reduced release of TNF-α or IL-6 (Comalada et al, 2006; Shanmugam et al., 2008). Moreover, oroxylin and wogonin displayed strong inhibitory effects on NF-κB and inducible nitric oxide synthase (iNOS). Flavonoids with *ortho*-dihydroxy substitution at the B-ring, such as quercetin, rhamnetin, fisetin and luteolin, significantly inhibited COX-2 expression (Mutoh et al., 2000). Quercetin, one of the most abundant dietary flavonols, showed anti-inflammatory effects triggered by modulation of several intracellular pathways. In human hepatoma HepG2 cells exposed to TNF-α, quercetin suppressed inflammation by down-regulating NF-κB, ERK, JNK and ROS; the expression of COX-2 was significantly reduced. In the same cell line, quercetin modulated p38-MAPK and Nrf2 in a concentration- and time-dependent manner. Besides, quercetin also increased glutathione level and up-regulated glutamylcysteine-synthetase, glutathione-peroxidase and glutathione-S-transferase. In BV-2 microglial cells, quercetin-induced Nrf2 stimulation led to up-regulation of the cytoprotective enzyme heme-oxygenase-1 (HO-1). Another important mechanism by which quercetin attenuates inflammation is inhibition of LPS-induced NO production. The flavonol kaempferol showed strong inhibitory effects against COX-1 and COX-2 isoenzymes (Ricciotti and Fitzgerald, 2011). Sheng et al. (2006) reported that the expression of genes involved in inflammation could be suppressed by kaempferol as well. Also, human liver cells treated with kaempferol showed a dose-dependent decline in the expression levels of iNOS and COX-2 (García-Mediavilla et al., 2007). Another

study by Huang et al. (2010) demonstrated that kaempferol significantly inhibited JNK and p38 phosphorylation, which were involved in the production of NO, and PGE2 and iNOS expressions. It is obvious that the purified flavone aglycones possess anti-inflammatory activities, but the impact of flavone glycosides in modulating inflammation is less explicit.

Flavone aglycones and flavone aglycone-rich extracts effectively reduced TNF-α production and inhibited the transcriptional activity of NF-κB, while glycoside-rich extracts showed no significant effects (Hostetler et al., 2012). For example, at 25 μM, flavone aglycones significantly reduced NF-κB activity, while the flavone glycosides (7-*O*-glucosides of apigenin and luteolin) showed no effect on TNF-α release or NF-κB activity even at high concentrations (100 μM) (Hostetler et al., 2012). After exposure to LPS, luteolin (IC_{50} = 8.7 μM) showed a stronger inhibitory effect on NO production than luteolin-7-*O*-glucoside (IC_{50} = 9.4 μM) without evoking toxicity (Hu and Kitts, 2004). Moreover, *ortho*-dihydroxy groups at the B-ring and a hydroxyl group at C-5 position on the A-ring significantly contribute to the anti-inflammatory activity (Amic et al., 2007). The anti-inflammatory activity of cynaroside (luteolin-7-*O*-β-D-glucoside) and cesioside (luteolin-7-O-β-D-primeveroside) was considerably reduced in comparison with luteolin (Odontuya et al., 2005). As aglycones are more active than the corresponding glycosides, the anti-inflammatory activity of flavonoids strongly depends on the deconjugation of its glycosides to aglycones. However, deglycosylation of flavone and flavonol glycosides will increase their cellular uptake ratios, thus the administration of dietary aglycones rather than their glycosides could lead to a more efficient uptake ratio into serum; meanwhile, higher lipophilicity of aglycones will facilitate their better penetration into the lipid membrane.

4.2. Flavanones and flavanonols

Flavanones are abundantly contained in citrus species. A previous study reported that eriodictyol and naringenin could reduce the expression of mRNA and the secretion of pro-inflammatory cytokines. Eriodictyol down-regulated NO production more effectively than naringenin (Huang et al., 2009). The anti-inflammatory activity of eriodictyol is predictable as eriodictyol has two hydroxyl groups at the C-3'- and C-4'-positions of the B-ring, whereas naringenin has only one hydroxyl group at the C-4'-position of the-ring B. Naringenin was also shown to reduce gene

expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and monocyte chemoattractant protein-1 (MCP-1) in endothelial cells (Chanet et al., 2013). In addition, naringin, the major flavanone glycoside in grapefruit, has been reported to enhance adiponectin transcription in differentiated 3T3-L1 adipocytes through the activation of PPAR-γ (Liu et al., 2008).

Among the flavanones, hesperetin differs from naringenin by the substitution of the C-4'-position on the B-ring with a methoxy group. This substitution appears to impair the ability of the flavanone to inhibit p38 phosphorylation and subsequent iNOS expression and NO release (Vafeiadou et al., 2009). Meanwhile, hesperidin and its aglycone hesperetin, augmented the ERK/Nrf2 signaling pathway as well as reduced inflammation (Parhiz et al., 2015). The study on structure-activity relationship showed that a lipophilic chain bound to 7-hydroxyl group (hesperetin) strongly influenced the anti-inflammatory effect (Parhiz et al., 2015). Besides, Lee et al. (2009) demonstrated that four hydroxylations at C-5, -7, -3' and -4' positions, together with a double bond at C2-C3 and the position of the B ring at C-2, are important for the anti-inflammatory activity of flavanones. A report of Patel et al. (2015) showed that 14 derivatives of 2'-hydroxy flavanone effectively reduced pro-inflammatory mediators (TNF-α, IL-1β and NO) in *in vitro* and *in vivo* models. Coincidentally, methoxylation at the C-3', -4', and -5' positions increased the inhibitory effect on NO production in LPS-stimulated macrophages (Lee, 2013). 2'-Hydroxy yokovanol and 2'-hydroxy neophellamuretin showed stronger inhibitory effects on IL-6 and TNF-α secretion than yokovanol and aromadendrin (Li et al., 2014). The result suggests that the anti-inflammatory activity is significantly improved when a hydroxyl group is bound to C-2' position of the skeleton.

4.3. Chalcones

Chalcones are widely distributed in fruits, vegetables, tea, spices, and soy based foodstuffs (Wu et al., 2011). Chemically, they consist of an open-chain flavonoid ring in which the two aryl rings are joined by a three carbon α- or β-unsaturated carbonyl bridge. Chalcones are basically intermediates in the synthesis of flavonoids (Dimmock et al., 1999). The presence of a double bond in conjugation with carbonyl functionality is believed to be responsible for the biological

activities of chalcones (Singh et al., 2014). Chalcones isolated from natural sources are well-known for anti-inflammatory properties and are promising for the development of anti-inflammatory drugs (Fang et al, 2015a; Gómez-Rivera et al., 2013; Hsieh et al., 2012). In addition, a series of chalcone derivatives, such as biscoumarin-chalcone hybrids and nitro chalcones, were designed and synthesized, and their anti-inflammatory potential was evaluated and confirmed (Sashidhara et al., 2011).

Chalcones exhibit anti-inflammatory activity by different mechanisms which are closely related to their chemical structure (Chamni and De-Eknamkul, 2013). A structure--activity relationship examination of chalcone analogues activities demonstrated that the presence of the unsaturated ketone moiety is critical for their activities (Larsen et al., 2005). Naringenin chalcone accumulates almost exclusively in peel of plants being converted into naringenin by chalcone isomerase. Naringenin chalcone exhibited significant anti-inflammatory properties by inhibiting pro-inflammatory mediators such as MCP-1 and TNF-α in LPS-stimulated RAW 264 macrophages and reducing iNOS expression (Muir et al., 2001). Hesperidin methyl chalcone inhibited carrageenan-induced cytokines (TNF-α, IL-1β, IL-6, and IL-10) production, oxidative stress, and NF-kB activation (Pinho-Ribeiro et al., 2015).

4.4. Anthocyaninins

Anthocyanins, glycosides of anthocyanidins, the most important group of water soluble pigments in nature, are responsible for the color of fruits (as berries, red grapes) and vegetables (purple sweet-potato, red cabbage). The ionic nature of anthocyanins enables changes of their structure according to the pH variation, resulting in different colors and hues (Figure 6A). The most important anthocyanidins (cyanidin, delphinidin, petunidin, peonidin, malvidin, and pelargonidin) differ by number and position of the hydroxyl groups on the flavan nucleus (Figure 6B). Recently, several authors have reported that anthocyanidins have anti-inflammatory effects by down-regulating the expression of COX-2, iNOS, and mRNA. Other studies showed that anthocyanidins effectively reduced mRNA and COX-2 expression by suppressing C/EBP, AP-1, and NF-κB in dose and structure-dependent manners (Hou et al., 2005). Besides, cyanidin-3-*O*-glucoside and anthocyanin fraction of blackberry extract reduced the expression/activity of iNOS

by attenuating NF-κB and/or MAPK activation (Pergola et al., 2006). Delphinidin exerts a significant anti-inflammatory activity by inhibiting the degradation of IkB-α, nuclear translocation of p65, and phosphorylation of JNK (Hou et al., 2005). Additionally, aside from antioxidant activity of anthocyanins, Wang et al. (2008) speculated that there should be some other signaling pathways involved in the anti-inflammatory activity induced by anthocyanins. For example, cyanidin-3-*O*-glucoside was reported to inhibit iNOS and COX-2 expressions by inducing liver X receptor α activation in THP-1 macrophages. Some other studies have reported that anthocyanins effectively up-regulate the signaling pathway of the nuclear receptors, such as liver X receptor α and PPARγ (Xia et al., 2006).

The structure-activity relationship studies indicated that *ortho*-dihydroxyphenyl structure on the B-ring of anthocyanidins is, at least, required to suppress COX-2 expression (Triebel et al., 2012). Many studies demonstrated that the number of hydroxyl groups on the B ring of anthocyanidins is also associated with the potency of their biological activities (Wang and Stoner, 2008; Xiao et al., 2008; Pereira et al., 2009). In general, *ortho*-dihydroxyphenyl anthocyanidins such as delphinidin and cyanidin showed powerful anti-inflammatory activity (Céspedes et al., 2010; Shih et al., 2007), while pelargonidin, peonidin, and malvidin lacking *ortho*-dihydroxyphenyl structure failed to show the above mentioned activities (Hou et al., 2005). Moreover, the number of hydroxyl groups on the B ring seems to influence the interactions between flavonoids and enzymes such as tyrosine kinase and protein kinase C, which are involved in the transcriptional activity of COX-2 (O'Leary et al., 2004). Indeed, a previous study reported by Hou et al. (2004) indicated that delphinidin, but not peonidin, could inhibit the activation of MAPKK (SEK and MEK) and MAPK (ERK and JNK), and consequently suppress AP-1 activation and cell transformation. A further study (Hou et al., 2005) confirmed that the *ortho*-dihydroxy structure of anthocyanidins (as shown in Figure 1) is essential for suppressing COX-2 expression and also critical for the inhibition of tyrosine kinase and protein kinase C.

4.5. Isoflavones

Isoflavones (3-phenylbenzopyran structure) are also generated by the phenylpropanoid pathway. Isoflavone synthase and isoflavone dehydratase are key enzymes involved in their biosynthesis

(Figure 2). Khan et al. (2012) reported that soy isoflavones significantly inhibited COX-2 expression, the production of proinflammatory cytokines and activation of NF-kB. Genistein and daidzein have been reported to down-regulate the inflammatory response (Wang et al., 2008). Chacko et al. (2005) demonstrated that the modulation of PPAR-γ pathway plays an important role in the anti-inflammatory activity of genistein. On the other hand, *in vivo* studies showed that the administration of daidzein suppressed inflammatory cytokine expression by the inhibition of NF-κB activation (Kim et al., 2009). However, isoflavones (genistein and daidzein) were found to be weaker anti-inflammatory agents as compared to flavonols (kaempferol and quercetin). Coincidentally, another study (Wang and Mazza, 2002) reported that kaempferol and quercetin were more effective in the suppression of NO production than genistein and genistin, and these two flavonols were stronger collagenase inhibitors than the corresponding flavones for treating skin inflammation (Sin and Kim, 2005). Taken together, these data suggest that C-3 hydroxyl substitution is important for the anti-inflammatory response. In consistence with these findings, irisolidone, tectorigenin, and glycetin suppressed LPS-induced release of NO and TNF-α in primary cultured microglia and BV2 microglial cell lines. Evaluation of structure-activity relationship indicated that 6-methoxylation contributed to the anti-inflammatory effect of isoflavones in the microglia (Park et al., 2006). Moreover, 4-methoxylation appears to enhance the activity; for example, irisolidone, having a 4-methoxy residue, showed a more potent anti-inflammatory effect as compared with other isoflavones. On the contrary, the glycosylated isoflavones (Figure 1) did not significantly suppress the inflammatory mediators, suggesting that glycosylation might decrease the biological activity. The anti-inflammatory effect of the aglycon was more potent than that of the glycoside form (Yuan et al., 2007).

4.6. Flavan-3-ols

Catechins belong to the flavan-3-ol subclass of flavonoids (Gadkari and Balaraman, 2015) and account for 60% up to 80% of the total flavonoids (Susanti et al., 2015) in fruits (cocoa, grapes, apricots, and cherries), beverages (tea and red wine) (Manach et al., 2004; Kondo et al., 2002), beans, and chocolate (Durácková and Knasmüller, 2007). Certain structural features (galloyl moiety on the C-ring and the number of hydroxyl groups on the B-ring) play a significant role in binding ability for proteins and other targets.

Catechins showed anti-inflammatory effects in both *in vivo* and *in vitro* studies (Maruyama et al., 2011). Their individual structural features, especially the presence of the galloyl moiety and hydroxyl groups but also the spatial arrangement (Trnková et al., 2013), together with their binding affinity to proteins and other targets such as lipids and cell surface (Fujimura et al., 2008; Sun et al., 2009), play an important role in their anti-inflammatory properties. The galloylated catechins (catechin gallate CG, epicatechin gallate ECG, gallocatechin gallate GCG, and epigallocatechin gallate EGCG) showed a significantly higher binding ability than the non-galloylated catechins (catechin C, epicatechin EC, gallocatechin GC, and epigallocatechin EGC) (Ishii et al., 2010). In addition, catechol-type catechins (ECG ≥ CG > EC ≥ C) possess a stronger binding affinity than pyragollol-type catechins (EGCG > GCG> GC > EGC). The binding affinity to serum albumin decreased in the following order: EG ≥ CG > EGCG > GCG >>EGC ≥ C > GC ≥ EC. These flavan-3-ols, especially EGCG, mediated inflammation through different mechanisms, such as inhibition of pro-inflammatory enzymes activity and scavenging of reactive oxygen and nitrogen (NO, peroxynitrite anion) species (Melgarejo et al., 2010; Zhong et al., 2012; Braicu et al., 2013; Marinovic et al., 2015). Consequently, the immunoreactivity of Ki-67 and CD-31, and α-smooth muscle actin expression were increased (Jang et al., 2015); the translocation of NF-kB from cytoplasm to nucleus was inhibited by blocking the phosphorylation of IκB- α and AP-1 (Negrão et al., 2013; Braicu et al., 2013). Finally, these reactions led to a reduction in the activities of COX-1, COX-2(Paquay et al., 2000; Nagai et al., 2002; Pandey & Rizvi, 2009) and iNOS (reduced expression of iNOS mRNA) (Zhao et al., 2012;). Oxidative stress (lipid peroxidation) are alleviated by decreasing the production of reactive oxygen species (hypochlorous acid, product of myeloperoxidase activity in neutrophils) (Nakano et al., 2012) and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) (Nakamura et al., 2010; Maruyama et al., 2011; Marzio et al., 2016).

5. Structural requirements for anti-inflammatory activity

Studies on a possible relationship between the structure of flavonoids and their anti-inflammatory effects are also summarized in the present review. As shown in Figure 7, hydroxylation on the C-3 position seems to diminish the anti-inflammatory effect. This activity could be compensated by the presence of other hydroxyl groups, as in case of quercetin

(Schneider et al., 2014). Further study reported by Lopez-Posadas et al. (2008) revealed that the presence of a C2–C3 double bond and hydroxyl groups at C-4', C-3' and C-5 positions enhanced the inhibitory effect on COX-2. In fact, the structural features required for the inhibition of p38 MAPK ERK, COX-2, and IL-2 were similar, reflecting a shared mechanism of anti-inflammatory activity (Lopez-Posadas et al. 2008). The reduction in NO production and inhibition of enzymes involved in the generation of prostaglandins and leukotrienes (phospholipase A2, 5- and 12-lipoxygenases) is also dependent on the presence of C2–C3 double bond (Costa et al., 2012). It was also demonstrated that flavones having C2–C3 double bond were more potent than homologous flavanones, which have a C2–C3 single bond (Gomes et al., 2013). On the other hand, the presence of a C2–C3 double bond is required for inhibiting ICAM-1 expression (Chen et al., 2016b). Moreover, the hydroxylation of the A-ring of flavonoids, in particular at C-5 and C-7 positions, proved to be favorable for the antioxidant activity, inhibition of NO production and cell adhesion molecules expression, such as ICAM-1 (Kim et al., 2004). However, the hydroxyl group at C-3 position slightly reduced the inhibitory effect on ICAM-1 expression (Takano-Ishikawa et al., 2003). 5, 7-Hydroxyflavone structure (apigenin, luteolin) seems to improve the inhibition of TNF production in RAW 264.7 cells (Gomes et al., 2008). Additionally, the presence of 8-methoxy group affected the inhibition of NO production (Benavente-Garcia and Castillo, 2008). The potency of *in vivo* anti-inflammatory activity of flavonoids depends on the pattern and number of hydroxyl groups on the B-ring. As the number of hydroxyl groups increases, the anti-inflammatory activity becomes stronger (Mastuda et al., 2002). For instance, catechol and guaiacol type structures having 3', 4'-dihydroxyl groups, are effective in inhibiting the granulomatous inflammation. Meanwhile, 3', 4'-dihydroxyl groups also promote inhibitory activity on TNF-α and NO production, and ICAM-1 expression (Kim et al., 2004). Finally, carbonyl group at C-4 position of the B-ring is required for the optimal inhibition of TNF-α-induced ICAM-1 expression (Sakakibara et al., 2003). Glycosylation also plays a critical role in the anti-inflammatory activity of flavonoids. For example, flavone aglycones are more potent in the reduction of TNF-α and inhibition of NF-κB transcriptional activity than the corresponding glycosides (luteolin *vs*. luteolin 7-*O*-glucoside) (Hostetler et al., 2012, Figure 8). The stronger inhibitory effect of aglycones on TNF-α and NF-κB activity has been stated by

other studies. Neither diosmetin 7-*O*-rutinoside nor apiin reduced NO and TNF-α in response to LPS, whereas apigenin effectively decreased the production of these inflammatory mediators (Shanmugam et al., 2008). In addition, due to hydrophilicity, flavonoid glycosides penetrate the cell membrane with difficulty.

6. Conclusions

Dietary flavonoids have the ability to attenuate inflammation by targeting different intracellular signaling pathways triggered by NF-κB, AP-1, PPAR, Nrf2, and MAPKs. Identification of the main structural features required for the modulation of these inflammation-related pathways (hydroxylation pattern, C2-C3 double bond) have an important role to play in the development of new anti-inflammatory drugs.

Acknowledgements

This research was supported by Major Projects of Science and Technology of Fujian Province (2014NZ0002-1), the construction project of top university at Fujian Agriculture and Forestry University of China (Grant No. 612014042 and Grant No. 612014043), the Start-up Research Grant from University of Macau (SRG2015-00061-ICMS-QRCM), and the opening fund of the State Key Laboratory of Quality Research in Chinese Medicine of University of Macau (No. SKL-QRCM-2014-2016).

References

Alcaraz, M. J., Vicente, A. M., Araico, A., Dominguez, J. N., Terencio, M. C., & Ferrándiz, M. L. (2004). Role of nuclear factor‐κB and heme oxygenase-1 in the mechanism of action of an anti‐inflammatory chalcone derivative in RAW 264.7 cells. *British Journal of Pharmacology*, *142*(7), 1191-1199.

Amic, D., Davidovic-Amic, D., Beslo, D., Rastija, V., Lucic, B., & Trinajstic, N. (2007). SAR and QSAR of the antioxidant activity of flavonoids. *Current Medicinal Chemistry*, *14*(7), 827-845.

Bandgar, B. P., Patil, S. A., Gacche, R. N., Korbad, B. L., Hote, B. S., Kinkar, S. N., & Jalde, S. S. (2010). Synthesis and biological evaluation of nitrogen-containing chalcones as possible anti-inflammatory and antioxidant agents. *Bioorganic & Medicinal Chemistry Letters*, *20*(2), 730-733.

Bandgar, B. P., Patil, S. A., Gacche, R. N., Korbad, B. L., Hote, B. S., Kinkar, S. N., & Jalde, S. S. (2010). Synthesis and biological evaluation of nitrogen-containing chalcones as possible anti-inflammatory and antioxidant agents. *Bioorganic & Medicinal Chemistry Letters*, *20*(2), 730-733.

Bauer, J., Kuehnl, S., Rollinger, J. M., Scherer, O., Northoff, H., Stuppner, H., & Koeberle, A. (2012). Carnosol and carnosic acids from Salvia officinalis inhibit microsomal prostaglandin E2 synthase-1. *Journal of Pharmacology and Experimental Therapeutics*, *342*(1), 169-176.

Benavente-Garcia, O., & Castillo, J. (2008). Update on uses and properties of citrus flavonoids: new findings in anticancer, cardiovascular, and anti-inflammatory activity. *Journal of Agricultural and Food Chemistry*, *56*(15), 6185-6205.

Boeck, P., Falcao, C. A. B., Leal, P. C., Yunes, R. A., Cechinel Filho, V., Torres-Santos, E. C., & Rossi-Bergmann, B. (2006). Synthesis of chalcone analogues with increased antileishmanial activity. *Bioorganic & Medicinal Chemistry*, *14*(5), 1538-1545.

Braicu, C., Ladomery, M. R., Chedea, V. S., Irimie, A., & Berindan-Neagoe, I. (2013). The relationship between the structure and biological actions of green tea catechins. *Food Chemistry*, *141*(3), 3282-3289.

Broom, O. J., Widjaya, B., Troelsen, J., Olsen, J., & Nielsen, O. H. (2009). Mitogen activated protein kinases: a role in inflammatory bowel disease?. *Clinical & Experimental Immunology*, *158*(3), 272-280.

Byun, E. B., Sung, N. Y., Byun, E. H., Song, D. S., Kim, J. K., Park, J. H., & Kim, J. H. (2013). The procyanidin trimer C1 inhibits LPS-induced MAPK and NF-κB signaling through TLR4 in macrophages. *International Immunopharmacology*, *15*(2), 450-456.

Cao H., Chen X. Q., Jassbi A. R., Xiao J. B. (2015). Microbial biotransformation of bioactive flavonoids. *Biotechnology Advances*, *33(1)*, 214-223.

Celinski, K., Dworzanski, T., Fornal, R., Korolczuk, A., Madro, A., & Slomka, M. (2012). Comparison of the anti-inflammatory and therapeutic actions of PPAR-gamma agonists rosiglitazone and troglitazone in experimental colitis. J Physiol Pharmacol, 63(6), 631-640.

Céspedes, C., Alarcon, J., Avila, J. G., & Nieto, A. (2010). Antiinflammatory activity of Aristotelia chilensis Mol.(Stuntz) (Elaeocarpaceae). *Boletín Latinoamericano y del Caribe de Plantas Medicinales y Aromáticas*, *9*(27), 127-135.

Chacko, B. K., Chandler, R. T., Mundhekar, A., Khoo, N., Pruitt, H. M., Kucik, D. F., & Patel, R. P. (2005). Revealing anti-inflammatory mechanisms of soy isoflavones by flow: modulation of leukocyte-endothelial cell interactions. *American Journal of Physiology-Heart and Circulatory Physiology*, *289*(2), H908-H915.

Chamni, S., & De-Eknamkul, W. (2013). Recent progress and challenges in the discovery of new neuraminidase inhibitors. *Expert Opinion on Therapeutic Patents*, *23*(4), 409-423.

Chandrashekar, N., Selvamani, A., Subramanian, R., Pandi, A., & Thiruvengadam, D. (2012). Baicalein inhibits pulmonary carcinogenesis-associated inflammation and interferes with COX-

2, MMP-2 and MMP-9 expressions in-vivo. *Toxicology and Applied Pharmacology*, *261*(1), 10-21.

Chanet, A., Milenkovic, D., Claude, S., Maier, J. A., Khan, M. K., Rakotomanomana, N., & Morand, C. (2013). Flavanone metabolites decrease monocyte adhesion to TNF-α-activated endothelial cells by modulating expression of atherosclerosis-related genes. *British Journal of Nutrition*, *110*(04), 587-598.

Che, H., Lim, H., Kim, H. P., & Park, H. (2011). A chrysin analog exhibited strong inhibitory activities against both PGE 2 and NO production. *European Journal of Medicinal Chemistry*, *46*(9), 4657-4660.

Chen, C. C., Hung, T. H., Wang, Y. H., Lin, C. W., Wang, P. Y., Lee, C. Y., & Chen, S. F. (2012). Wogonin improves histological and functional outcomes, and reduces activation of TLR4/NF-κB signaling after experimental traumatic brain injury. *PloS one*, *7*(1), e30294.

Chen, L., & Kang, Y. H. (2013). Anti-inflammatory and antioxidant activities of red pepper (Capsicum annuum L.) stalk extracts: Comparison of pericarp and placenta extracts. *Journal of Functional Foods*, *5*(4), 1724-1731.

Chen, L., & Kang, Y. H. (2014). Antioxidant and Enzyme Inhibitory Activities of Plebeian Herba (Salvia plebeia R. Br.) under Different Cultivation Conditions. *Journal of agricultural and food chemistry*, *62*(10), 2190-2197.

Chen, L., Kang, Y. H., & Suh, J. K. (2014). 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 Research International*, *56*, 236-242.

Chen, L., Teng, H., Fang, T., & Xiao, J.B. (2016). Agrimonolide from Agrimonia pilosa suppresses inflammatory responses through down-regulation of COX-2/iNOS and inactivation of NF-κB in lipopolysaccharide-stimulated macrophages. *Phytomedicine*, *23*(8), 846-855.

Chen, L., Teng, H., Xie, Z., Cao, H., Cheang, W. S., Skalicka-Woniak, K. & Xiao, J. (2016). Modifications of dietary flavonoids towards improved bioactivity: An update on structure-

activity rRelationship. *Critical Reviews in Food Science and Nutrition*, doi: 10.1080/10408398.2016.1196334.

Chen, S. (2011). Natural products triggering biological targets-a review of the anti-inflammatory phytochemicals targeting the arachidonic acid pathway in allergy asthma and rheumatoid arthritis. *Current Drug Targets*, *12*(3), 288-301.

Chen, W. P., Wang, Y. L., Tang, J. L., Hu, P. F., Bao, J. P., & Wu, L. D. (2012). Morin inhibits interleukin-1β-induced nitric oxide and prostaglandin E 2 production in human chondrocytes. *International Immunopharmacology*, *12*(2), 447-452.

Chen, W., Ge, X., Xu, F., Zhang, Y., Liu, Z., Pan, J., & Liang, G. (2015). Design, synthesis and biological evaluation of paralleled Aza resveratrol--chalcone compounds as potential anti-inflammatory agents for the treatment of acute lung injury. *Bioorganic & Medicinal Chemistry Letters*, *25*(15), 2998-3004.

Chen, Y. C., Shen, S. C., Lee, W. R., Hou, W. C., Yang, L. L., & Lee, T. J. (2001). Inhibition of nitric oxide synthase inhibitors and lipopolysaccharide induced inducible NOS and cyclooxygenase‐2 gene expressions by rutin, quercetin, and quercetin pentaacetate in RAW 264.7 macrophages. *Journal of Cellular Biochemistry*, *82*(4), 537-548.

Chiba Y, Ogita T, Ando K, Fujita T. PPAR gamma ligands inhibit TNF-alpha-induced LOX-1 expression in cultured endothelial cells. Biochem Biophys Res Commun, 2001, 286, 541-6.

Chien, S. T., Lin, S. S., Wang, C. K., Lee, Y. B., Chen, K. S., Fong, Y., & Shih, Y. W. (2011). Acacetin inhibits the invasion and migration of human non-small cell lung cancer A549 cells by suppressing the p38α MAPK signaling pathway. *Molecular and Cellular Biochemistry*, *350*(1-2), 135-148.

Cianciulli, A., Calvello, R., Cavallo, P., Dragone, T., Carofiglio, V., & Panaro, M. A. (2012). Modulation of NF-κB activation by resveratrol in LPS treated human intestinal cells results in downregulation of PGE 2 production and COX-2 expression. *Toxicology in Vitro*, *26*(7), 1122-1128.

Clarke, D., Damera, G., Sukkar, M. B., & Tliba, O. (2009). Transcriptional regulation of cytokine function in airway smooth muscle cells. *Pulmonary Pharmacology & Therapeutics*, *22*(5), 436-445.

Comalada, M., Ballester, I., Bailon, E., Sierra, S., Xaus, J., Galvez, J., & Zarzuelo, A. (2006). Inhibition of pro-inflammatory markers in primary bone marrow-derived mouse macrophages by naturally occurring flavonoids: analysis of the structure--activity relationship. Biochemical pharmacology,72(8), 1010-1021.

Costa, G., Francisco, V., C Lopes, M., T Cruz, M., & T Batista, M. (2012). Intracellular signaling pathways modulated by phenolic compounds: application for new anti-inflammatory drugs discovery. *Current Medicinal Chemistry*, *19*(18), 2876-2900.

Cui, Y., Yang, X., Lu, X., Chen, J., & Zhao, Y. (2014). Protective effects of polyphenols-enriched extract from Huangshan Maofeng green tea against CCl 4-induced liver injury in mice.g*Chemico-biological interactions*,hemico-biologDi

Dinkova-Kostova, A. T., Holtzclaw, W. D., & Kensler, T. W. (2005). The role of Keap1 in cellular protective responses. *Chemical Research in Toxicology*,*18*(12), 1779-1791.

Donà, M., Dell'Aica, I., Calabrese, F., Benelli, R., Morini, M., Albini, A., & Garbisa, S. (2003). Neutrophil restraint by green tea: inhibition of inflammation, associated angiogenesis, and pulmonary fibrosis. *The Journal of Immunology*, *170*(8), 4335-4341.

Ďuračková, Z., & Knasmüller, S. (2007). The Activity of Natural Compounds in diseases prevention and therapy.. *Slovak Academic Press, Bratislava*, 2007

Elias, D. W., Beazely, M. A., & Kandepu, N. M. (1999). Bioactivities of chalcones. *Current Medicinal Chemistry*, *6*(12), 1125.

Eo, H. J., Park, J. H., Park, G. H., Lee, M. H., Lee, J. R., Koo, J. S., & Jeong, J. B. (2014). Anti-inflammatory and anti-cancer activity of mulberry (Morus alba L.) root bark. *BMC Complementary and Alternative Medicine*, *14*(1), 1.

Erlund, I. (2004). Review of the flavonoids quercetin, hesperetin, and naringenin. Dietary sources, bioactivities, bioavailability, and epidemiology. *Nutrition Research, 24(10),* 851-874.

Fan, G. W., Zhang, Y., Jiang, X., Zhu, Y., Wang, B., Su, L., & Gao, X. (2013). Anti-inflammatory activity of baicalein in LPS-stimulated RAW264. 7 macrophages via estrogen receptor and NF-κB-dependent pathways. *Inflammation*, *36*(6), 1584-1591.

Fang, Q., Wang, J., Wang, L., Zhang, Y., Yin, H., Li, Y., & Zheng, C. (2015). Attenuation of inflammatory response by a novel chalcone protects kidney and heart from hyperglycemia-induced injuries in type 1 diabetic mice.*Toxicology and applied pharmacology*, *288*(2), 179-191.

Fang, Q., Zhao, L., Wang, Y., Zhang, Y., Li, Z., Pan, Y., & Liang, G. (2015). A novel chalcone derivative attenuates the diabetes-induced renal injury via inhibition of high glucose-mediated inflammatory response and macrophage infiltration. *Toxicology and Applied Pharmacology*, *282*(2), 129-138.

Fernandes, I., Faria, A; de Freitas, V., Calhau, C., & Mateus, N. (2015). Multiple-approach studies to assess anthocyanin bioavailability. *Phytochemistry Reviews, 14(6),* 899-919.

Ferreyra, M. L. F., Rius, S. P., & Casati P. (2012). Flavonoids: biosynthesis, biological functions, and biotechnological applications. *Frontiers in Plant Science*, doi: 10.3389/fpls.2012.00222.

Fujimura, Y., Umeda, D., Yamada, K., & Tachibana, H. (2008). The impact of the 67kDa laminin receptor on both cell-surface binding and anti-allergic action of tea catechins. *Archives of Biochemistry and Biophysics*, *476*(2), 133-138.

Funakoshi-Tago, M., Nakamura, K., Tago, K., Mashino, T., & Kasahara, T. (2011). Anti-inflammatory activity of structurally related flavonoids, Apigenin, Luteolin and Fisetin. *International Immunopharmacology*, *11*(9), 1150-1159.

Gadkari, P. V., & Balaraman, M. (2015). Catechins: sources, extraction and encapsulation: a review. *Food and Bioproducts Processing, 93,* 122-138.

García-Mediavilla, V., Crespo, I., Collado, P. S., Esteller, A., Sánchez-Campos, S., Tuñón, M. J., & 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. *European Journal of Pharmacology*,*557*(2), 221-229.

George, V. C., Vijesh, V. V., Dehigaspege, A. I., Lakshmi, C. A., Anbarasu, K., Kumar, D. R.,, Ethiraj, R., Kumar, R. A., & Rupasinghe, H. P. (2016). Mechanism of Action of Flavonoids in Prevention of Inflammation-Associated Skin Cancer. *Curr Med Chem., 23(32),* 3697

Gladine, C., Morand, C., Rock, E., Bauchart, D., & Durand, D. (2007). Plant extracts rich in polyphenols (PERP) are efficient antioxidants to prevent lipoperoxidation in plasma lipids from animals fed n-3 PUFA supplemented diets.t*Animal Feed Science and Technology*,nimal Feed Science

Gleichenhagen, M., & Schieber, A. (2016). Current challenges in polyphenol analytical chemistry. *Current Opinion in Food Science*, *7*, 43-49.

Gomes, A., Fernandes, E., Lima, J. L., Mira, L., & Corvo, M. L. (2008). Molecular mechanisms of anti-inflammatory activity mediated by flavonoids. *Current Medicinal Chemistry*, *15*(16), 1586-1605.

Gómez-Rivera, A., Aguilar-Mariscal, H., Romero-Ceronio, N., Roa-de la Fuente, L. F., & Lobato-García, C. E. (2013). Synthesis and anti-inflammatory activity of three nitro chalcones. *Bioorganic & Medicinal Chemistry Letters*, *23*(20), 5519-5522.

Gonzalez, R., Ballester, I., Lopez-Posadas, R., Suarez, M. D., Zarzuelo, A., Martinez-Augustin, O., & Medina, F. S. D. (2011). Effects of flavonoids and other polyphenols on inflammation. *Critical reviews in food science and nutrition*, *51*(4), 331-362.

Gopalakrishnan, A., & Kong, A. N. T. (2008). Anticarcinogenesis by dietary phytochemicals: cytoprotection by Nrf2 in normal cells and cytotoxicity by modulation of transcription factors NF-κB and AP-1 in abnormal cancer cells.*Food and Chemical Toxicology*, *46*(4), 1257-1270.

Grover, J., & Jachak, S. M. (2015). Coumarins as privileged scaffold for anti-inflammatory drug development. *RSC Advances*, *5*(49), 38892-38905.

Ha, J., Zhao, L., Zhao, Q., Yao, J., Zhu, B. B., Lu, N., & Guo, Q. L. (2012). Oroxylin A improves the sensitivity of HT-29 human colon cancer cells to 5-FU through modulation of the COX-2 signaling pathway. *Biochemistry and Cell Biology*, *90*(4), 521-531.

Ha, S. K., Moon, E., Ju, M. S., Kim, D. H., Ryu, J. H., Oh, M. S., & Kim, S. Y. (2012). 6-Shogaol, a ginger product, modulates neuroinflammation: A new approach to neuroprotection. *Neuropharmacology*, *63*(2), 211-223.

Harikumar, K. B., Sung, B., Tharakan, S. T., Pandey, M. K., Joy, B., Guha, S., Aggarwal, B. B. (2010). Sesamin manifests chemopreventive effects through the suppression of NF-κB--regulated cell survival, proliferation, invasion, and angiogenic gene products. *Molecular Cancer Research*, *8*(5), 751-761.

Hostetler, G., Riedl, K., Cardenas, H., Diosa-Toro, M., Arango, D., Schwartz, S., & Doseff, A. I. (2012). Flavone deglycosylation increases their anti-inflammatory activity and absorption. *Molecular Nutrition & Food Research*, *56*(4), 558-569.

Hou, D. X., Kai, K., Li, J. J., Lin, S., Terahara, N., Wakamatsu, M., & Colburn, N. (2004). Anthocyanidins inhibit activator protein 1 activity and cell transformation: structure--activity relationship and molecular mechanisms.*Carcinogenesis*, *25*(1), 29-36.

Hou, D. X., Yanagita, T., Uto, T., Masuzaki, S., & Fujii, M. (2005). Anthocyanidins inhibit cyclooxygenase-2 expression in LPS-evoked macrophages: structure--activity relationship and molecular mechanisms involved. *Biochemical pharmacology*, *70*(3), 417-425.

Hsieh, C. T., Hsieh, T. J., El-Shazly, M., Chuang, D. W., Tsai, Y. H., Yen, C. T., & Chang, F. R. (2012). Synthesis of chalcone derivatives as potential anti-diabetic agents. *Bioorganic & Medicinal Chemistry Letters*, *22*(12), 3912-3915.

Hsieh, T. P., Sheu, S. Y., Sun, J. S., & Chen, M. H. (2011). Icariin inhibits osteoclast differentiation and bone resorption by suppression of MAPKs/NF-κB regulated HIF-1α and PGE 2 synthesis. *Phytomedicine*, *18*(2), 176-185.

Hu, C., & Kitts, D. D. (2004). Luteolin and luteolin-7-O-glucoside from dandelion flower suppress iNOS and COX-2 in RAW264.7 cells. *Molecular and Cellular Biochemistry*, *265*(1-2), 107-113.

Huan, S. K. H., Wang, K. T., Yeh, S. D., Lee, C. J., Lin, L. C., Liu, D. Z., & Wang, C. C. (2012). Scutellaria baicalensis alleviates cantharidin-induced rat hemorrhagic cystitis through inhibition of cyclooxygenase-2 overexpression. *Molecules*, *17*(6), 6277-6289.

Huang, C. H., Jan, R. L., Kuo, C. H., Chu, Y. T., Wang, W. L., Lee, M. S., & Hung, C. H. (2010). Natural Flavone Kaempferol Suppresses Chemokines Expression in Human Monocyte THP‐1 Cells through MAPK Pathways.*Journal of Food Science*, *75*(8), H254-H259.

Huang, D. W., Chung, C. P., Kuo, Y. H., Lin, Y. L., & Chiang, W. (2009). Identification of compounds in adlay (Coix lachryma-jobi L. var. ma-yuen Stapf) seed hull extracts that inhibit lipopolysaccharide-induced inflammation in RAW 264.7 macrophages. *Journal of Agricultural and Food Chemistry*, *57*(22), 10651-10657.

Hwang, Y. P., Choi, J. H., Yun, H. J., Han, E. H., Kim, H. G., Kim, J. Y., Jeong, H. G. (2011). Anthocyanins from purple sweet potato attenuate dimethylnitrosamine-induced liver injury in rats by inducing Nrf2-mediated antioxidant enzymes and reducing COX-2 and iNOS expression. *Food and Chemical Toxicology*, *49*(1), 93-99.

Ikigai, H., Nakae, T., Hara, Y., & Shimamura, T. (1993). Bactericidal catechins damage the lipid bilayer. *Biochimica et Biophysica Acta (BBA)-Biomembranes*, *1147*(1), 132-136.

Ishii, T., Minoda, K., Bae, M. J., Mori, T., Uekusa, Y., Ichikawa, T., & Nakayama, T. (2010). Binding affinity of tea catechins for HSA: Characterization by high‐performance affinity chromatography with immobilized albumin column. *Molecular Nutrition & Food Research*, *54*(6), 816-822.

Itoh, K., Tong, K. I., & Yamamoto, M. (2004). Molecular mechanism activating Nrf2--Keap1 pathway in regulation of adaptive response to electrophiles. *Free Radical Biology and Medicine*, *36*(10), 1208-1213.

Iwanaga, K., Okada, M., Murata, T., Hori, M., & Ozaki, H. (2012). Prostaglandin E2 promotes wound-induced migration of intestinal subepithelial myofibroblasts via EP2, EP3, and EP4 prostanoid receptor activation. *Journal of Pharmacology and Experimental Therapeutics*, *340*(3), 604-611.

Jang, M. Y., Lee, Y. L., Long, C. Y., Chen, C. H., Chuang, S. M., Lee, H. Y., & Juan, Y. S. (2015). The protective effect of green tea catechins on ketamine-induced cystitis in a rat model. *Urological Science*, *26*(3), 186-192.

Jeong, C. W., Yoo, K. Y., Lee, S. H., Jeong, H. J., Lee, C. S., & Kim, S. J. (2012). Curcumin protects against regional myocardial ischemia/reperfusion injury through activation of RISK/GSK-3β and inhibition of p38 MAPK and JNK.*Journal of cardiovascular pharmacology and therapeutics*, *17*(4), 387-394.

Jeong, J. B., Hong, S. C., Jeong, H. J., & Koo, J. S. (2011). Anti-inflammatory effect of 2-methoxy-4-vinylphenol via the suppression of NF-κB and MAPK activation, and acetylation of histone H3. *Archives of Pharmacal Research*,*34*(12), 2109-2116.

Jeong, J. B., Hong, S. C., Jeong, H. J., & Koo, J. S. (2011). Anti-inflammatory effect of 2-methoxy-4-vinylphenol via the suppression of NF-κB and MAPK activation, and acetylation of histone H3. *Archives of pharmacal research*,*34*(12), 2109-2116.

Jiang C, Ting AT, Seed B. PPAR-gamma agonists inhibit production of monocyte inflammatory cytokines. Nature, 1998, 391, 82-6.

Jung, K. A., & Kwak, M. K. (2010). The Nrf2 system as a potential target for the development of indirect antioxidants. *Molecules*, *15*(10), 7266-7291.

Kaminska, B. (2005). MAPK signalling pathways as molecular targets for anti-inflammatory therapy---from molecular mechanisms to therapeutic benefits.*Biochimica et Biophysica Acta (BBA)-Proteins and Proteomics*, *1754*(1), 253-262.

Kang, S. R., Park, K. I., Park, H. S., Lee, D. H., Kim, J. A., Nagappan, A., & Han, D. Y. (2011). Anti-inflammatory effect of flavonoids isolated from Korea Citrus aurantium L. on lipopolysaccharide-induced mouse macrophage RAW 264.7 cells by blocking of nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) signalling pathways. *Food Chemistry*, *129*(4), 1721-1728.

Kawakita, Y., Ikekita, M., Kurozumi, R., & Kojima, S. (2003). Increase of Intracellular Glutathione by Low-Dose. GAMMA.-Ray Irradiation Is Mediated by Transcription Factor AP-1 in RAW 264.7 Cells. *Biological and Pharmaceutical Bulletin*, *26*(1), 19-23.

Kensler, T. W., Wakabayashi, N., & Biswal, S. (2007). Cell survival responses to environmental stresses via the Keap1-Nrf2-ARE pathway. *Annu. Rev. Pharmacol. Toxicol.*, *47*, 89-116.

Khan, A. Q., Khan, R., Rehman, M. U., Lateef, A., Tahir, M., Ali, F., & Sultana, S. (2012). Soy isoflavones (daidzein & genistein) inhibit 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced cutaneous inflammation via modulation of COX-2 and NF-κB in Swiss albino mice. *Toxicology*, *302*(2), 266-274.

Kim, A. R., Lee, M. S., Shin, T. S., Hua, H., Jang, B. C., Choi, J. S., & Kim, H. R. (2011). Phlorofucofuroeckol A inhibits the LPS-stimulated iNOS and COX-2 expressions in macrophages via inhibition of NF-κB, Akt, and p38 MAPK. *Toxicology in Vitro*, *25*(8), 1789-1795

Kim, H. P., Son, K. H., Chang, H. W., & Kang, S. S. (2004). Anti-inflammatory plant flavonoids and cellular action mechanisms. *Journal of Pharmacological Sciences*, *96*(3), 229-245.

Kim, H. S., Kim, M. J., Kim, E. J., Yang, Y., Lee, M. S., & Lim, J. S. (2012). Berberine-induced AMPK activation inhibits the metastatic potential of melanoma cells via reduction of ERK activity and COX-2 protein expression. *Biochemical Pharmacology*, *83*(3), 385-394.

Kim, J. W., Jin, Y. C., Kim, Y. M., Rhie, S., Kim, H. J., Seo, H. G., & Chang, K. C. (2009). Daidzein administration in vivo reduces myocardial injury in a rat ischemia/reperfusion model by inhibiting NF-kB activation. *Life sciences*, *84*(7), 227-234

Kim, J., Cha, Y. N., & Surh, Y. J. (2010). A protective role of nuclear factor-erythroid 2-related factor-2 (Nrf2) in inflammatory disorders. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *690*(1), 12-23.

Kim, Y. J. (2013). Rhamnetin attenuates melanogenesis by suppressing oxidative stress and pro-inflammatory mediators. *Biological and Pharmaceutical Bulletin*, *36*(8), 1341-1347.

Kondo, S., Tsuda, K., Muto, N., & Ueda, J. E. (2002). Antioxidative activity of apple skin or flesh extracts associated with fruit development on selected apple cultivars. *Scientia Horticulturae*, *96*(1), 177-185.

Kwon, S. H., Kim, J. A., Hong, S. I., Jung, Y. H., Kim, H. C., Lee, S. Y., & Jang, C. G. (2011). Loganin protects against hydrogen peroxide-induced apoptosis by inhibiting phosphorylation of JNK, p38, and ERK 1/2 MAPKs in SH-SY5Y cells. *Neurochemistry International*, *58*(4), 533-541.

Kumar, S., & Pandey, A. K. (2013). Chemistry and Biological Activity of Flavonoids: An Overview. *The Scientific World Journal*, http://dx.doi.org/10.1155/2013/162750.

Larsen, M., Kromann, H., Kharazmi, A., & Nielsen, S. F. (2005). Conformationally restricted anti-plasmodial chalcones. *Bioorganic & Medicinal Chemistry Letters*, *15*(21), 4858-4861.

Lau, G. T. Y., Huang, H., Lin, S. M., & Leung, L. K. (2010). Butein downregulates phorbol 12-myristate 13-acetate-induced COX-2 transcriptional activity in cancerous and non-cancerous breast cells. *European Journal of Pharmacology*, *648*(1), 24-30.

Lee, W. K., Chung, K. W., Kim, G. H., & Kim, S. J. (2013). Gallotannin causes differentiation and inflammation via ERK-1/-2 and p38 kinase pathways in rabbit articular chondrocytes. *Molecular Medicine Reports*, *7*(2), 701-707.

Li, F., Nitteranon, V., Tang, X., Liang, J., Zhang, G., Parkin, K. L., & Hu, Q. (2012). In vitro antioxidant and anti-inflammatory activities of 1-dehydro-(6)-gingerdione, 6-shogaol, 6-dehydroshogaol and hexahydrocurcumin. *Food Chemistry*, *135*(2), 332-337.

Li, Q., & Verma, I. M. (2002). NF-κB regulation in the immune system. *Nature Reviews Immunology*, *2*(10), 725-734.

Li, W., Sun, Y. N., Yan, X. T., Yang, S. Y., Kim, S., Chae, D., & Kim, Y. H. (2014). Anti-inflammatory and antioxidant activities of phenolic compounds from Desmodium caudatum leaves and stems. *Archives of Pharmacal Research*,*37*(6), 721-727.

Li, X., Han, Y., Guan, Y., Zhang, L., Bai, C., & Li, Y. (2012). Aluminum induces osteoblast apoptosis through the oxidative stress-mediated JNK signaling pathway. *Biological trace element research*, *150*(1-3), 502-508.

Li, Y. S., Wu, L. P., Li, K. B., Liu, Y. P., Xiang, R., Zhang, S. B., & Zhang, L. Y. (2011). Involvement of nuclear factor κB (NF-κB) in the downregulation of cyclo-oxygenase-2 (COX-2) by genistein in gastric cancer cells. *Journal of International Medical Research*, *39*(6), 2141-2150.

Lim, R., Barker, G., Wall, C. A., & Lappas, M. (2013). Dietary phytophenols curcumin, naringenin and apigenin reduce infection-induced inflammatory and contractile pathways in human placenta, foetal membranes and myometrium. *Molecular Human Reproduction*, *19*(7), 451-462.

Liu, B., Jian, Z., Li, Q., Li, K., Wang, Z., Liu, L., & Gao, T. (2012). Baicalein protects human melanocytes from H_2O_2-inuced apoptosis via inhibiting mitochondria-dependent caspase activation and the p38 MAPK pathway. *Free Radical Biology and Medicine*, *53*(2), 183-193.

Liu, L., Shan, S., Zhang, K., Ning, Z. Q., Lu, X. P., & Cheng, Y. Y. (2008). Naringenin and hesperetin, two flavonoids derived from *Citrus aurantium* up‐regulate transcription of adiponectin. *Phytotherapy Research*, *22*(10), 1400-1403.

Liu, M., Wilairat, P., & Go, M. L. (2002). Antimalarial Alkoxylated and Hydroxylated Chalcones: Structure-Activity Relationship Analysis. *Journal of Medicinal Chemistry*, *45*(8), 1735-1735.

Lopez-Posadas R, Ballester I, Abadia-Molina AC, Suarez MD, Zarzuelo A, Martinez-Augustin O, Sanchez de Medina F (2008). Effect of flavonoids on rat splenocytes, a structure- activity relationship study. Biochem Pharmacol 76: 495-506.

Loizzo M.R., Pugliese A., Bonesi M., Tenuta M.C., Menichini F., Xiao J.B., Tundis R. (2016). Edible flowers: A rich source of phytochemicals with antioxidant and hypoglycaemic activity. Journal of Agricultural and Food Chemistry, 64(12), 2467-2474.

Lu, Y., Yang, J. H., Li, X., Hwangbo, K., Hwang, S. L., Taketomi, Y., & Chang, H. W. (2011). Emodin, a naturally occurring anthraquinone derivative, suppresses IgE-mediated anaphylactic reaction and mast cell activation. *Biochemical pharmacology*, *82*(11), 1700-1708.

Luca, V. S.; Miron, A.; Aprotosoaie, A.C. (2016). The antigenotoxic potential of dietary flavonoids. *Phytochemistry Reviews*, 15(4), 591-625.

Manach, C., Scalbert, A., Morand, C., Rémésy, C., & Jiménez, L. (2004). Polyphenols: food sources and bioavailability. *The American Journal of Clinical Nutrition*, *79*(5), 727-747.

Marín, L., Miguélez, E. M., Villar, C. J., & Lombó, F. (2015). Bioavailability of Dietary Polyphenols and Gut Microbiota Metabolism: Antimicrobial Properties. *BioMed Research International*, 2015:905215

Marinovic, M. P., Morandi, A. C., & Otton, R. (2015). Green tea catechins alone or in combination alter functional parameters of human neutrophils via suppressing the activation of TLR-4/NFκB p65 signal pathway. *Toxicology in Vitro*, *29*(7), 1766-1778.

Marzio, L., Ventura, C. A., Cosco, D., Paolino, D., Di Stefano, A., Stancanelli, R., & Fresta, M. (2016). Nanotherapeutics for anti-inflammatory delivery. *Journal of Drug Delivery Science and Technology*, *32*, 174-191.

Maruyama, T., Tomofuji, T., Endo, Y., Irie, K., Azuma, T., Ekuni, D., & Morita, M. (2011). Supplementation of green tea catechins in dentifrices suppresses gingival oxidative stress and periodontal inflammation. *Archives of Oral Biology*, *56*(1), 48-53.

Mastuda, H., Morikawa, T., Ueda, K., Managi, H., & Yoshikawa, M. (2002). Structural requirements of flavonoids for inhibition of antigen-induced degranulation, TNF-α and IL-4 production from RBL-2H3 cells. *Bioorganic & Medicinal Chemistry*, *10*(10), 3123-3128.

Melgarejo, E., Medina, M. Á., Sánchez-Jiménez, F., & Urdiales, J. L. (2010). Targeting of histamine producing cells by EGCG: a green dart against inflammation? *Journal of Physiology and Biochemistry*, *66*(3), 265-270.

Menezes, J.C., Orlikova, B., Morceau, F., Diederich, M. (2016). Natural and synthetic flavonoids: Structure-activity relationship and chemotherapeutic potential for the treatment of leukemia. *Crit Rev Food Sci Nutr*., 56(S1), S4-S28.

Mo, N., Li, Z. Q., Li, J., & Cao, Y. D. (2012). Curcumin inhibits TGF-β1-induced MMP-9 and invasion through ERK and Smad signaling in breast cancer MDA-MB-231 cells. *Asian Pacific Journal of Cancer Prevention*, *13*(11), 5709-5714

Muir, S. R., Collins, G. J., Robinson, S., Hughes, S., Bovy, A., De Vos, C. R., & Verhoeyen, M. E. (2001). Overexpression of petunia chalcone isomerase in tomato results in fruit containing increased levels of flavonols. *Nature Biotechnology*, *19*(5), 470-474.

Mustapa, A. N., Martin, A., Gallego, J. R., Mato, R. B., & Cocero, M. J. (2015). Microwave-assisted extraction of polyphenols from Clinacanthus nutans Lindau medicinal plant: Energy perspective and kinetics modeling.Chemical Engineering and Processing: Process Intensification,sed 66-74.

Mutoh, M., Takahashi, M., Fukuda, K., Komatsu, H., Enya, T., Matsushima‐Hibiya, Y., & Wakabayashi, K. (2000). Suppression by Flavonoids of Cyclooxygenase‐2 Promoter‐dependent Transcriptional Activity in Colon Cancer Cells: Structure‐Activity Relationship. *Japanese Journal of Cancer Research*, *91*(7), 686-691.

Nagai, K., Jiang, M. H., Hada, J., Nagata, T., Yajima, Y., Yamamoto, S., & Nishizaki, T. (2002). (−)-Epigallocatechin gallate protects against NO stress-induced neuronal damage after ischemia by acting as an anti-oxidant. *Brain Research*, *956*(2), 319-322.

Nakamura, H., Ukai, T., Yoshimura, A., Kozuka, Y., Yoshioka, H., Yoshinaga, Y., & Hara, Y. (2010). Green tea catechin inhibits lipopolysaccharide‐induced bone resorption in vivo. *Journal of Periodontal Research*, *45*(1), 23-30.

Nakano, T., Masuda, M., Suzuki, T., & Ohshima, H. (2012). Inhibition by polyphenolic phytochemicals and sulfurous compounds of the formation of 8-chloroguanosine mediated by hypochlorous acid, human myeloperoxidase, and activated human neutrophils. *Bioscience, Biotechnology, and Biochemistry*, *76*(12), 2208-2213.

Negrão, R., Costa, R., Duarte, D., Gomes, T. T., Azevedo, I., & Soares, R. (2013). Different effects of catechin on angiogenesis and inflammation depending on VEGF levels. *The Journal of Nutritional Biochemistry*, *24*(2), 435-444.

Nworu, C. S., & Akah, P. A. (2015). Anti-inflammatory medicinal plants and the molecular mechanisms underlying their activities. *African Journal of Traditional, Complementary and Alternative Medicines*, *12*(s1), 52-61.

O'Leary, K. A., de Pascual-Tereasa, S., Needs, P. W., Bao, Y. P., O'Brien, N. M., & Williamson, G. (2004). Effect of flavonoids and vitamin E on cyclooxygenase-2 (COX-2) transcription. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*, *551*(1), 245-254.

Odontuya, G., Hoult, J. R. S., & Houghton, P. J. (2005). Structure-activity relationship for antiinflammatory effect of luteolin and its derived glycosides. *Phytotherapy research*, *19*(9), 782-786.

Ou, K., & Gu, L. (2014). Absorption and metabolism of proanthocyanidins. *Journal of Functional Foods*, *7*, 43-53.

Owuor, E. D., & Kong, A. N. T. (2002). Antioxidants and oxidants regulated signal transduction pathways. *Biochemical Pharmacology*, *64*(5), 765-770.

Özdemir, A., Altıntop, M. D., Turan-Zitouni, G., Çiftçi, G. A., Ertorun, I., Alataş, Ö., & Kaplancıklı, Z. A. (2015). Synthesis and evaluation of new indole-based chalcones as potential antiinflammatory agents. *European journal of Medicinal Chemistry*, *89*, 304-309.

Pandey, K. B., & Rizvi, S. I. (2009). Plant polyphenols as dietary antioxidants in human health and disease. *Oxidative Medicine and Cellular Longevity*, *2*(5), 270-278.

Paquay, J. B., Haenen, G. R., Stender, G., Wiseman, S. A., Tijburg, L. B., & Bast, A. (2000). Protection against nitric oxide toxicity by tea. *Journal of Agricultural and Food Chemistry*, *48*(11), 5768-5772.

Parhiz, H., Roohbakhsh, A., Soltani, F., Rezaee, R., & Iranshahi, M. (2015). Antioxidant and Anti‐Inflammatory Properties of the Citrus Flavonoids Hesperidin and Hesperetin: An Updated Review of their Molecular Mechanisms and Experimental Models. *Phytotherapy Research*, *29*(3), 323-331.

Park, M. Y., Kwon, H. J., & Sung, M. K. (2009). Evaluation of aloin and aloe-emodin as anti-inflammatory agents in aloe by using murine macrophages. *Bioscience, Biotechnology, and Biochemistry*, *73*(4), 828-832.

Park, S. E., Sapkota, K., Kim, S., Kim, H., & Kim, S. J. (2011). Kaempferol acts through mitogen‐activated protein kinases and protein kinase B/AKT to elicit protection in a model of neuroinflammation in BV2 microglial cells. *British Journal of Pharmacology*, *164*(3), 1008-1025.

Patel, N. K., Bairwa, K., Gangwal, R., Jaiswal, G., Jachak, S. M., Sangamwar, A. T., & Bhutani, K. K. (2015). 2′-Hydroxy flavanone derivatives as an inhibitors of pro-inflammatory mediators: Experimental and molecular docking studies. *Bioorganic & medicinal chemistry letters*, *25*(9), 1952-1955.

Pearson, G., Robinson, F., Beers Gibson, T., Xu, B. E., Karandikar, M., Berman, K., & Cobb, M. H. (2001). Mitogen-activated protein (MAP) kinase pathways: regulation and physiological functions 1. *Endocrine Reviews*, *22*(2), 153-183.

Pereira, D. M., Valentão, P., Pereira, J. A., & Andrade, P. B. (2009). Phenolics: From Chemistry to Biology. *Molecules*, *14*(6), 2202-2211.

Pergola, C., Rossi, A., Dugo, P., Cuzzocrea, S., & Sautebin, L. (2006). Inhibition of nitric oxide biosynthesis by anthocyanin fraction of blackberry extract. *Nitric Oxide*, *15*(1), 30-39.

Pesce, M., Franceschelli, S., Ferrone, A., De Lutiis, M. A., Patruno, A., Grilli, A., & Speranza, L. (2015). Verbascoside down-regulates some pro-inflammatory signal transduction pathways by increasing the activity of tyrosine phosphatase SHP‐1 in the U937 cell line. *Journal of Cellular and Molecular Medicine*, *19*(7), 1548-1556.

Pinho-Ribeiro, F. A., Hohmann, M. S., Borghi, S. M., Zarpelon, A. C., Guazelli, C. F., Manchope, M. F., & Verri, W. A. (2015). Protective effects of the flavonoid hesperidin methyl chalcone in inflammation and pain in mice: Role of TRPV1, oxidative stress, cytokines and NF-κB. *Chemico-biological Interactions*, *228*, 88-99.

Procházková, D., Boušová, I., & Wilhelmová, N. (2011). Antioxidant and prooxidant properties of flavonoids. *Fitoterapia*, *82*, 513-523.

Qi, Z., Yin, F., Lu, L., Shen, L., Qi, S., Lan, L., & Yin, Z. (2013). Baicalein reduces lipopolysaccharide-induced inflammation via suppressing JAK/STATs activation and ROS production. *Inflammation Research*, *62*(9), 845-855.

Qiao, H., Zhang, X., Zhu, C., Dong, L., Wang, L., Zhang, X., & Cao, X. (2012). Luteolin downregulates TLR4, TLR5, NF-κB and p-p38MAPK expression, upregulates the p-ERK expression, and protects rat brains against focal ischemia. *Brain research*, *1448*, 71-81.

Ricciotti, E., & FitzGerald, G. A. (2011). Prostaglandins and inflammation. *Arteriosclerosis, Thrombosis, and Vascular biology*, *31*(5), 986-1000.

Ricote M, Huang JT, Welch JS, Glass CK. The peroxisome proliferator-activated receptor (PPAR gamma) as a regulator of monocyte/macrophage function. J Leukoc Biol, 1999, 66, 733-739.

Rozmer, Z., Perjesi, P. (2016). Naturally occurring chalcones and their biological activities. Phytochemistry Reviews, 15(1), 87-120.

Sakakibara, H., Honda, Y., Nakagawa, S., Ashida, H., & Kanazawa, K. (2003). Simultaneous determination of all polyphenols in vegetables, fruits, and teas. *Journal of Agricultural and Food Chemistry*, *51*(3), 571-581.

Sakulnarmrat, K., Fenech, M., Thomas, P., & Konczak, I. (2013). Cytoprotective and pro-apoptotic activities of native Australian herbs polyphenolic-rich extracts. *Food Chemistry*, 2013, 136, 9-17.

Sashidhara, K. V., Kumar, M., Modukuri, R. K., Sonkar, R., Bhatia, G., Khanna, A. K., Rai, S., & Shukla, R. (2011). Synthesis and anti-inflammatory activity of novel biscoumarin--chalcone hybrids. *Bioorganic & Medicinal Chemistry Letters*, *21*(15), 4480-4484.

Sato, K., Mihara, Y., Kanai, K., Yamashita, Y., Kimura, Y., & Itoh, N. (2016). Tyrosol ameliorates lipopolysaccharide-induced ocular inflammation in rats via inhibition of nuclear factor (NF)-κB activation. *Journal of Veterinary Medical Science*, 78(9), 1429-1438.

Schneider, M. J., Abdel-Aziz, H., & Efferth, T. (2014). Phytochemicals for the treatment of inflammatory bowel diseases. *Phytochemistry Reviews*, *13*(3), 629-642.

Seo, E. J., Ngoc, T. M., Lee, S. M., Kim, Y. S., & Jung, Y. S. (2012). Chrysophanol-8-O-glucoside, an anthraquinone derivative in rhubarb, has antiplatelet and anticoagulant activities. *Journal of Pharmacological Sciences*, *118*(2), 245-254.

Shanmugam, K., Holmquist, L., Steele, M., Stuchbury, G., Berbaum, K., Schulz, O., & Dobson, G. (2008). Plant‐derived polyphenols attenuate lipopolysaccharide‐induced nitric oxide and tumour necrosis factor production in murine microglia and macrophages. *Molecular Nutrition & Food Research*, *52*(4), 427-438.

Sheng, W. Y., Chen, Y. R., & Wang, T. C. V. (2006). A major role of PKC θ and NFκB in the regulation of hTERT in human T lymphocytes. *FEBS Letters*, *580*(30), 6819-6824.

Shih, P. H., Yeh, C. T., & Yen, G. C. (2007). Anthocyanins induce the activation of phase II enzymes through the antioxidant response element pathway against oxidative stress-induced apoptosis. *Journal of Agricultural and Food Chemistry*, *55*(23), 9427-9435.

Sin, B. Y., & Kim, H. P. (2005). Inhibition of collagenase by naturally-occurring flavonoids. *Archives of Pharmacal Research*, *28*(10), 1152-1155.

Singh, B. N., Shankar, S., & Srivastava, R. K. (2011). Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. *Biochemical Pharmacology*, *82*(12), 1807-1821.

Singh, P., Anand, A., & Kumar, V. (2014). Recent developments in biological activities of chalcones: A mini review. *European Journal of Medicinal Chemistry*, *85*, 758-777.

Singh, T., & Katiyar, S. K. (2011). Honokiol, a phytochemical from Magnolia spp., inhibits breast cancer cell migration by targeting nitric oxide and cyclooxygenase-2. *International Journal of Oncology*, *38*(3), 769.

Soetikno, V., Sari, F. R., Lakshmanan, A. P., Arumugam, S., Harima, M., Suzuki, K., & Watanabe, K. (2013). Curcumin alleviates oxidative stress, inflammation, and renal fibrosis in remnant kidney through the Nrf2--keap1 pathway. *Molecular Nutrition & Food Research*, *57*(9), 1649-1659.

Son, J. K., Son, M. J., Lee, E., Moon, T. C., Son, K. H., Kim, C. H., & Chang, H. W. (2005). Ginkgetin, a biflavone from *Ginko biloba* leaves, inhibits cyclooxygenases-2 and 5-lipoxygenase in mouse bone marrow-derived mast cells. *Biological and Pharmaceutical Bulletin*, *28*(12), 2181-2184.

Song, L., Zhao, J., Zhang, X., Li, H., & Zhou, Y. (2013). Icariin induces osteoblast proliferation, differentiation and mineralization through estrogen receptor-mediated ERK and JNK signal activation. *European Journal of Pharmacology*, *714*(1), 15-22.

Sun, Y., Hung, W. C., Chen, F. Y., Lee, C. C., & Huang, H. W. (2009). Interaction of tea catechin (---)-epigallocatechin gallate with lipid bilayers.*Biophysical Journal*, *96*(3), 1026-1035.

Susanti, E., Ratnawati, R., & Rudijanto, A. (2015). Qualitative analysis of catechins from green tea GMB-4 clone using HPLC and LC-MS/MS. *Asian Pacific Journal of Tropical Biomedicine*, *5*(12), 1046-1050.

Takano-Ishikawa, Y., Goto, M., & Yamaki, K. (2003). Inhibitory effects of several flavonoids on E‐selectin expression on human umbilical vein endothelial cells stimulated by tumor necrosis factor-α. *Phytotherapy Research*, *17*(10), 1224-1227.

Talalay, P., & Fahey, J. W. (2001). Phytochemicals from cruciferous plants protect against cancer by modulating carcinogen metabolism. *The Journal of Nutrition*, *131*(11), 3027S-3033S

Teng, H., Chen, L., Huang, Q., Wang, J., Lin, Q., Liu, M., & Song, H. (2016). Ultrasonic-Assisted Extraction of Raspberry Seed Oil and Evaluation of Its Physicochemical Properties, Fatty Acid Compositions and Antioxidant Activities.*PloS one*, *11*(4), e0153457.

Triebel, S., Trieu, H. L., & Richling, E. (2012). Modulation of inflammatory gene expression by a bilberry (Vaccinium myrtillus L.) extract and single anthocyanins considering their limited stability under cell culture conditions.*Journal of Agricultural and Food Chemistry*, *60*(36), 8902-8910.

Trnková, L., Ricci, D., Grillo, C., Colotti, G., & Altieri, F. (2013). Green tea catechins can bind and modify ERp57/PDIA3 activity. *Biochimica et Biophysica Acta (BBA)-General Subjects*, *1830*(3), 2671-2682.

Undurti N., Das, M.D., F.A.M.S., F.R.S.C. (2013). Catechins and osteoporosis. *Nutrition*, 29, 697-699.

Vafeiadou, K., Vauzour, D., Lee, H. Y., Rodriguez-Mateos, A., Williams, R. J., & Spencer, J. P. (2009). The citrus flavanone naringenin inhibits inflammatory signalling in glial cells and protects against neuroinflammatory injury. *Archives of Biochemistry and Biophysics*, *484*(1), 100-109.

Vanden Berghe, W., De Naeyer, A., Dijsselbloem, N., David, J. P., De Keukeleire, D., & Haegeman, G. (2011). Attenuation of ERK/RSK2-driven NFκB gene expression and cancer cell proliferation by kurarinone, a lavandulyl flavanone isolated from Sophora flavescens Ait. roots. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders)*, *11*(3), 247-261.

Vona-Davis, L., Yu, A., Magabo, K., Evans, T., Jackson, B., Riggs, D., & McFadden, D. (2004). Peptide YY attenuates transcription factor activity in tumor necrosis factor-alpha-induced pancreatitis. Journal of the American College of Surgeons, 199(1), 87-95.

Wang, J., & Mazza, G. (2002). Inhibitory effects of anthocyanins and other phenolic compounds on nitric oxide production in LPS/IFN-γ-activated RAW 264.7 macrophages. *Journal of Agricultural and Food Chemistry*, *50*(4), 850-857.

Wang, J., Zhang, Q., Jin, S., He, D., Zhao, S., & Liu, S. (2008). Genistein modulate immune responses in collagen-induced rheumatoid arthritis model. *Maturitas*, *59*(4), 405-412.

Wang, L. S., & Stoner, G. D. (2008). Anthocyanins and their role in cancer prevention. *Cancer Letters*, *269*(2), 281-290.

Wang, Q., Han, P. H., Zhang, M. W., Xia, M., Zhu, H. L., Ma, J., & Ling, W. H. (2007). Supplementation of black rice pigment fraction improves antioxidant and anti-inflammatory status in patients with coronary heart disease. *Asia Pacific journal of clinical nutrition*, *16*(S1), 295-301.

Wang, S. T., Yang, H., Gao, W., Li, H. J., & Li, P. (2016). Trace enrichment and characterization of polyphenols in Bistort Rhizoma using weak anion-exchange solid phase extraction and high performance liquid chromatography-quadrupole time-of-flight mass spectrometry. *W., Li, H. J., & Li, P. (2016). Trace enrichment*,ang, S. T., YWang, Y., Yang, Q., Yan, J. T., Zhao, C., Cianflone, K., & Wang, D. W. (2006). Effects of bezafibrate on the expression of endothelial nitric oxide synthase gene and its mechanisms in cultured bovine endothelial cells.Atherosclerosis,and high performa

Warat, M., Szliszka, E., Korzonek-Szlacheta, I., Król, W., & Czuba, Z. P. (2014). Chrysin, Apigenin and Acacetin Inhibit Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand Receptor-1 (TRAIL-R1) on Activated RAW264. 7 Macrophages. *International Journal of Molecular Sciences*, *15*(7), 11510-11522.

Weng, C. J., & Yen, G. C. (2015). Natural plant extracts as antioxidants for food preservation. *Handbook of Antioxidants for Food Preservation*, 235.

Weng, C. J., Chen, M. J., Yeh, C. T., & Yen, G. C. (2011). Hepatoprotection of quercetin against oxidative stress by induction of metallothionein expression through activating MAPK and PI3K pathways and enhancing Nrf2 DNA-binding activity. *New Biotechnology*, *28*(6), 767-777.

Wu, J., Zhang, Y., Cai, Y., Wang, J., Weng, B., Tang, Q., & Yang, S. (2013). Discovery and evaluation of piperid-4-one-containing mono-carbonyl analogs of curcumin as anti-inflammatory agents. *Bioorganic & Medicinal Chemistry*, *21*(11), 3058-3065.

Xagorari, A., Roussos, C., & Papapetropoulos, A. (2002). Inhibition of LPS‐stimulated pathways in macrophages by the flavonoid luteolin. *British Journal of Pharmacology*, *136*(7), 1058-1064.

Xia, X., Ling, W., Ma, J., Xia, M., Hou, M., Wang, Q., & Tang, Z. (2006). An anthocyanin-rich extract from black rice enhances atherosclerotic plaque stabilization in apolipoprotein E-deficient mice. *The Journal of Nutrition*, *136*(8), 2220-2225.

Xiao, J.B., Suzuki, M., Jiang, X.Y., Chen, X.Q., Yamamoto, K., Ren, F.L., & Xu, M. (2008). Influence of B-ring hydroxylation on interactions of flavonols with bovine serum albumin. *Journal of Agricultural and Food Chemistry*, *56*(7), 2350-2356.

Xiao, J.B., Capanoglu E., Jassbi A.R., Miron A. (2016). Advance on the flavonoid C-glycosides and health benefits. *Critical Reviews in Food Science and Nutrition*, 56, S29-S45.

Xiao, J.B. (2017). Dietary flavonoid aglycones and their glycosides: What show better biological benefits? *Critical Reviews in Food Science and Nutrition*, 57(6),

Xiao J.B., Muzashvili T.S., Georgiev M.I. (2014). Advance on biotechnology for glycosylation of high-value flavonoids. *Biotechnology Advances*, *32*, 1145-1156.

Xiao J.B., & Högger P. (2014). Influence of diabetes on the pharmacokinetic behavior of natural polyphenols. *Current Drug Metabolism*, *15*, 23-29.

Xiao, J.B., Ni, X.L., Kai, G.Y., Chen, X.Q. (2015). Advance in dietary polyphenols as aldose reductases inhibitors: Structure-activity relationship aspect. *Critical Reviews in Food Science and Nutrition*, 55(1), 16-31.

Xiao, J.B., Högger, P. (2015). Dietary polyphenols and type 2 diabetes: current insights and future perspectives. *Current Medicinal Chemistry*, 22(1), 23-38.

Xu, X., Zhou, X. D., & Wu, C. D. (2011). The tea catechin epigallocatechin gallate suppresses cariogenic virulence factors of Streptococcus mutans. *Antimicrobial agents and chemotherapy*, *55*(3), 1229-1236.

Yamauchi, K., Mitsunaga, T., Inagaki, M., & Suzuki, T. (2014). Synthesized quercetin derivatives stimulate melanogenesis in B16 melanoma cells by influencing the expression of melanin biosynthesis proteins MITF and p38 MAPK. *Bioorganic & Medicinal Chemistry*, *22*(13), 3331-3340.

Yang, H. J., Youn, H., Seong, K. M., Yun, Y. J., Kim, W., Kim, Y. H., & Youn, B. (2011). Psoralidin, a dual inhibitor of COX-2 and 5-LOX, regulates ionizing radiation (IR)-induced pulmonary inflammation. *Biochemical pharmacology*, *82*(5), 524-534.

Yang, Y., Tan, Y. X., Chen, R. Y., & Kang, J. (2014). The latest review on the polyphenols and their bioactivities of Chinese Morus plants. *Journal of Asian Natural Products Research*, *16*(6), 690-702.

Yeh, C. H., Yang, J. J., Yang, M. L., Li, Y. C., & Kuan, Y. H. (2014). Rutin decreases lipopolysaccharide-induced acute lung injury via inhibition of oxidative stress and the MAPK--NF-κB pathway. *Free Radical Biology and Medicine*, *69*, 249-257.

Ying, T. H., Yang, S. F., Tsai, S. J., Hsieh, S. C., Huang, Y. C., Bau, D. T., & Hsieh, Y. H. (2012). Fisetin induces apoptosis in human cervical cancer HeLa cells through ERK1/2-mediated activation of caspase-8-/caspase-3-dependent pathway. *Archives of Toxicology*, *86*(2), 263-273.

Yoon, H. Y., Lee, E. G., Lee, H., Cho, I. J., Choi, Y. J., Sung, M. S., & Yoo, W. H. (2013). Kaempferol inhibits IL-1β-induced proliferation of rheumatoid arthritis synovial fibroblasts and the production of COX-2, PGE2 and MMPs. *International Journal of Molecular Medicine*, *32*(4), 971-977.

Yu, J. S., & Kim, A. K. (2011). Wogonin induces apoptosis by activation of ERK and p38 MAPKs signaling pathways and generation of reactive oxygen species in human breast cancer cells. *Molecules and Cells*, *31*(4), 327-335.

Yuan, J. P., Wang, J. H., & Liu, X. (2007). Metabolism of dietary soy isoflavones to equol by human intestinal microflora-implications for health. *Molecular Nutrition & Food Research*, *51*(7), 765-781.

Zhan, K., Xu, K., & Yin, H. (2011). Preparative separation and purification of gingerols from ginger (Zingiber officinale Roscoe) by high-speed counter-current chromatography. *Food Chemistry*, *126*(4), 1959-1963.

Zhang, X., Wang, G., Gurley, E. C., & Zhou, H. (2014). Flavonoid apigenin inhibits lipopolysaccharide-induced inflammatory response through multiple mechanisms in macrophages. *PLoS One*, *9*(9), e107072.

Zhang, Y., Zhao, C., He, W., Wang, Z., Fang, Q., Xiao, B., & Yang, S. (2014). Discovery and evaluation of asymmetrical monocarbonyl analogs of curcumin as anti-inflammatory agents. *Drug Design, Develop Therapy*, *8*, 373.

Zhao, Y., Jiang, F., Liu, P., Chen, W., & Yi, K. (2012). Catechins containing a galloyl moiety as potential anti-HIV-1 compounds. *Drug Discovery Today*, *17*(11), 630-635.

Zhong, P., Wu, L., Qian, Y., Fang, Q., Liang, D., Wang, J., & Liang, G. (2015). Blockage of ros and NF-κB-mediated inflammation by a new chalcone l6h9 protects cardiomyocytes from

hyperglycemia-induced injuries.*Biochimica et Biophysica Acta (BBA)-Molecular Basis of Disease*, *1852*(7), 1230-1241.

Zhong, Y., Chiou, Y. S., Pan, M. H., & Shahidi, F. (2012). Anti-inflammatory activity of lipophilic epigallocatechin gallate (EGCG) derivatives in LPS-stimulated murine macrophages. *Food Chemistry*, *134*(2), 742-748.

Table 1. Intracellular signaling pathways/mediators associated with inflammation modulated by flavonoids (studies performed over 2011-2015)

Effect on inflammatory signaling pathways	Flavonoids	Ref.
↓ p38 MAPK activation	hesperidin, naringin, nobiletin, icariin, baicalein, luteolin, rutin, quercetin, quercetin derivative	Kim et al., 2011; Kang et al., 2011; Song et al., 2013; Liu et al., 2012; Qiao et al., 2012; Yeh et al., 2014; Weng et al., 2011; Yamauchi et al., 2014
↓ ERK activation	apigenin, fisetin, luteolin, acacetin	Zhang et al., 2014; Ying et al., 2012; Funakoshi-Tago et al., 2011; Warat et al., 2014
↓ JNK activation	quercetin, luteolin, rutin, kaempferol	Weng et al., 2011; Qiao et al., 2012; Yeh et al., 2014; Park et al., 2011
↓ LPS-induced MAPK and NF-κB signaling	procyanidin trimer C1	Byun et al., 2013
↓ mRNA level of COX-2	butein, baicalein, wogonin, naringenin, apigenin, acacetin, oroxylin, quercetin, isoquercetin, icarrin derivative	Lau et al., 2010; Chen et al., 2012; Lim et al., 2013; Chen et al., 2011; Ha et al., 2012; Hsieh et al., 2011; Chandrashekar et al., 2012;
↓ COX-2 protein	naringenin, baicalein, wogonin, genistein, quercetin, kaempferol, rutin	Lim et al., 2013; Qi et al., 2013; Yu et al., 2011; Li et al., 2011; Weng et al., 2011; Park et al., 2011; Yeh et al., 2014
↓ COX-2 activity	icariin, sangennon D, morusin, epigallocatechin gallate, catechin, epicatechin, catechin gallate, peicatechin gallate, gallocatechin, epigallocatechin	Hsieh et al., 2011; Yang et al., 2014; Eo et al., 2014; Zhong et al., 2012; Singh et al., 2011
↓ prostaglandin E2	morin, wogonin, acacetin, oroxylin, genistein, baicalein, baicalin, kaempferol, chrysin	Chen et al., 2012; Chien et al., 2011; Huan et al., 2012; Iwanaga et al., 2012; Fan et al., 2013; Yoon et al., 2013; Che et al., 2011
↓ thromboxane B2	rhamnetin	Kim, 2013
↓ prostaglandin D2	bilobetin, ginkgetin	Nworu and Akah, 2015

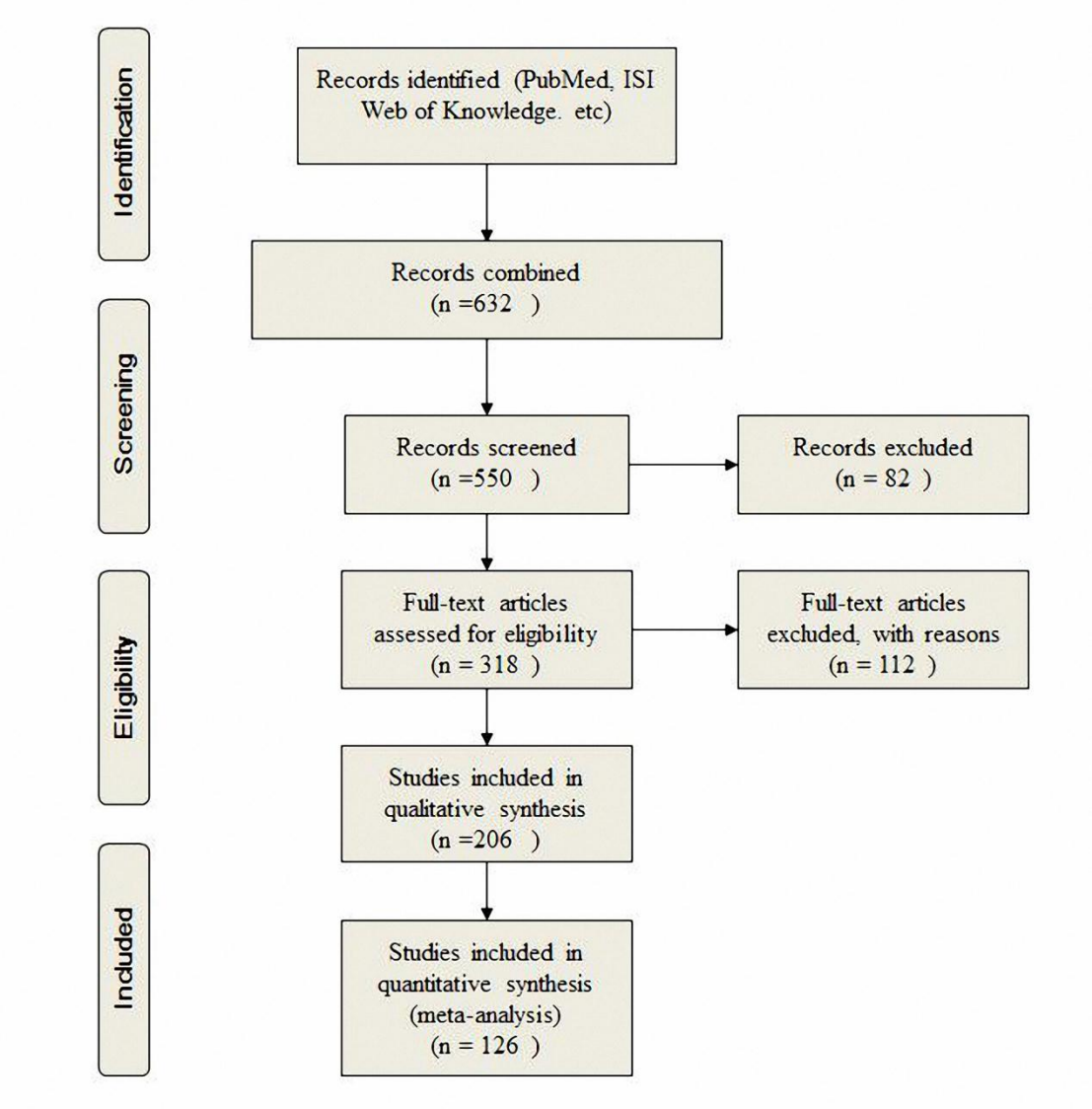


Figure 1. Schematic overview of the search strategy for this review.

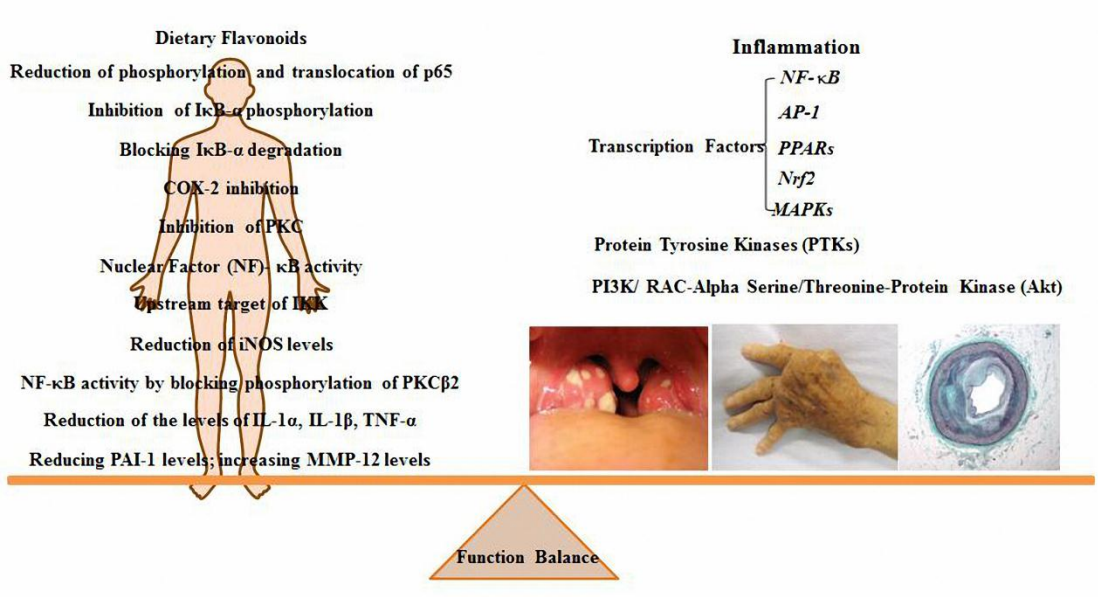


Figure 2. On the left side of the balance, intake of flavonoid containing diet could keep the function balance of the body by reducing phosphorylation of p65, inhibiting IkB-α phosphorylation COX-2, and PKC, blocking IkB-α degradation etc.
On the right side of the balance the increased immunogenic antigen exposure, prompting inflammatory cytokine production of nuclear factor (NF)-kB, activator protein (AP)-1, peroxisome proliferator-activated receptor (PPAR) and nuclear factor erythroid 2-related factor 2 (Nrf2) transcription factors; mitogen-activated protein kinases (MAPKs) resulted in inflammation.

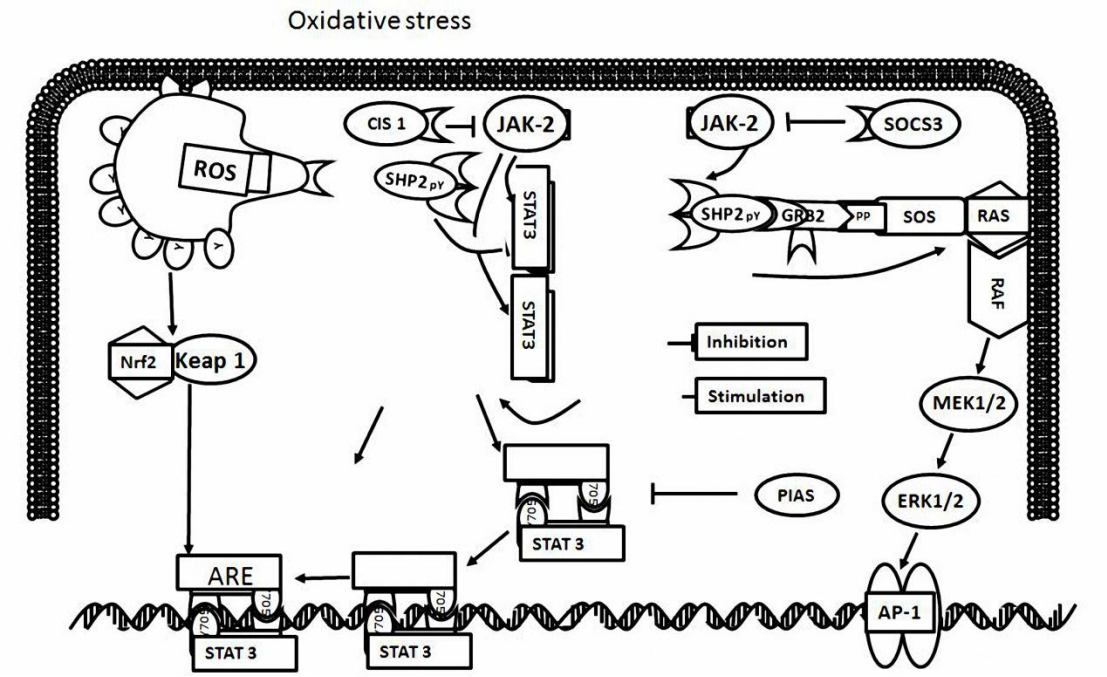
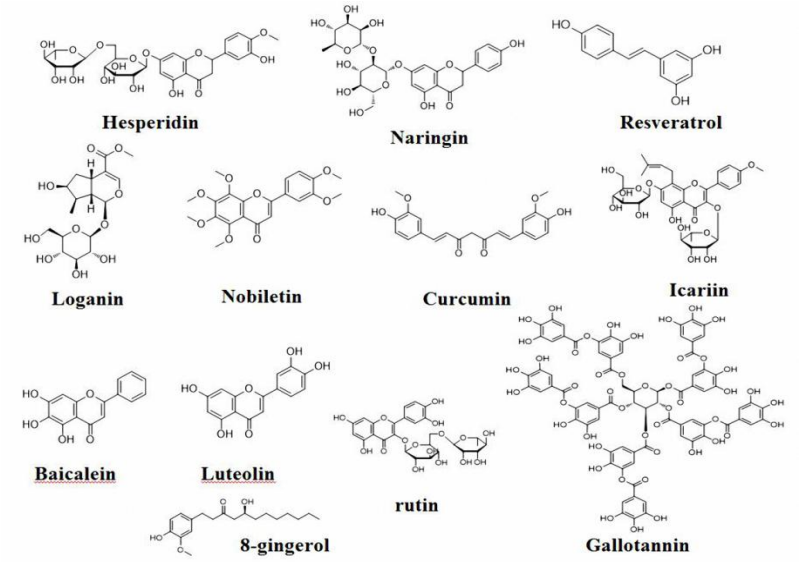
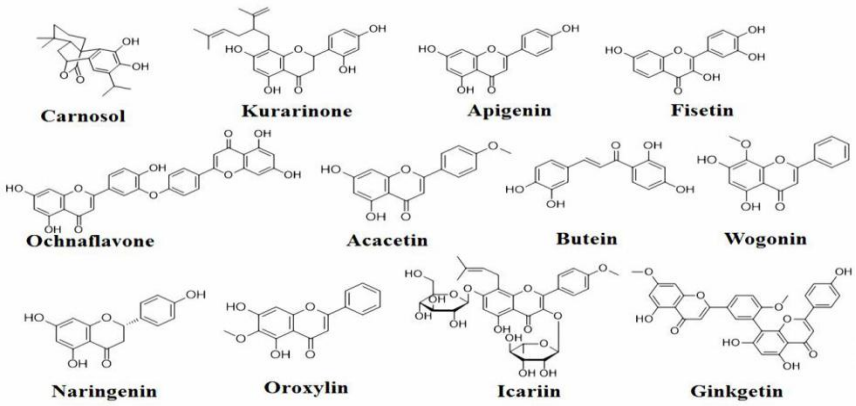
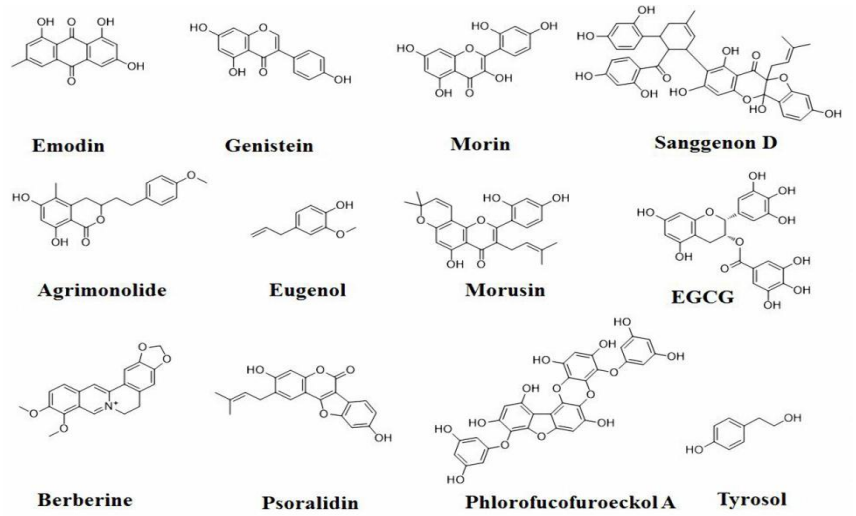


Figure 3. Inflammatory intracellular signaling pathways modulated by flavonoid compounds. Akt, RAC-alpha serine/threonine-protein kinase; ARE, antioxidant response element; ERK, extracellular signal-regulated kinase; iNOS, inducible nitric oxide synthase; Keap1, kelch-like ECH-associated protein 1; MAPK, mitogen-activated protein kinase; MKK and MEK, MAPK kinase kinase; Nrf2, nuclear factor erythroid 2-related factor 2; JAK/STAT, Janus Kinase/ Signal Transducer and Activator of Transcription.







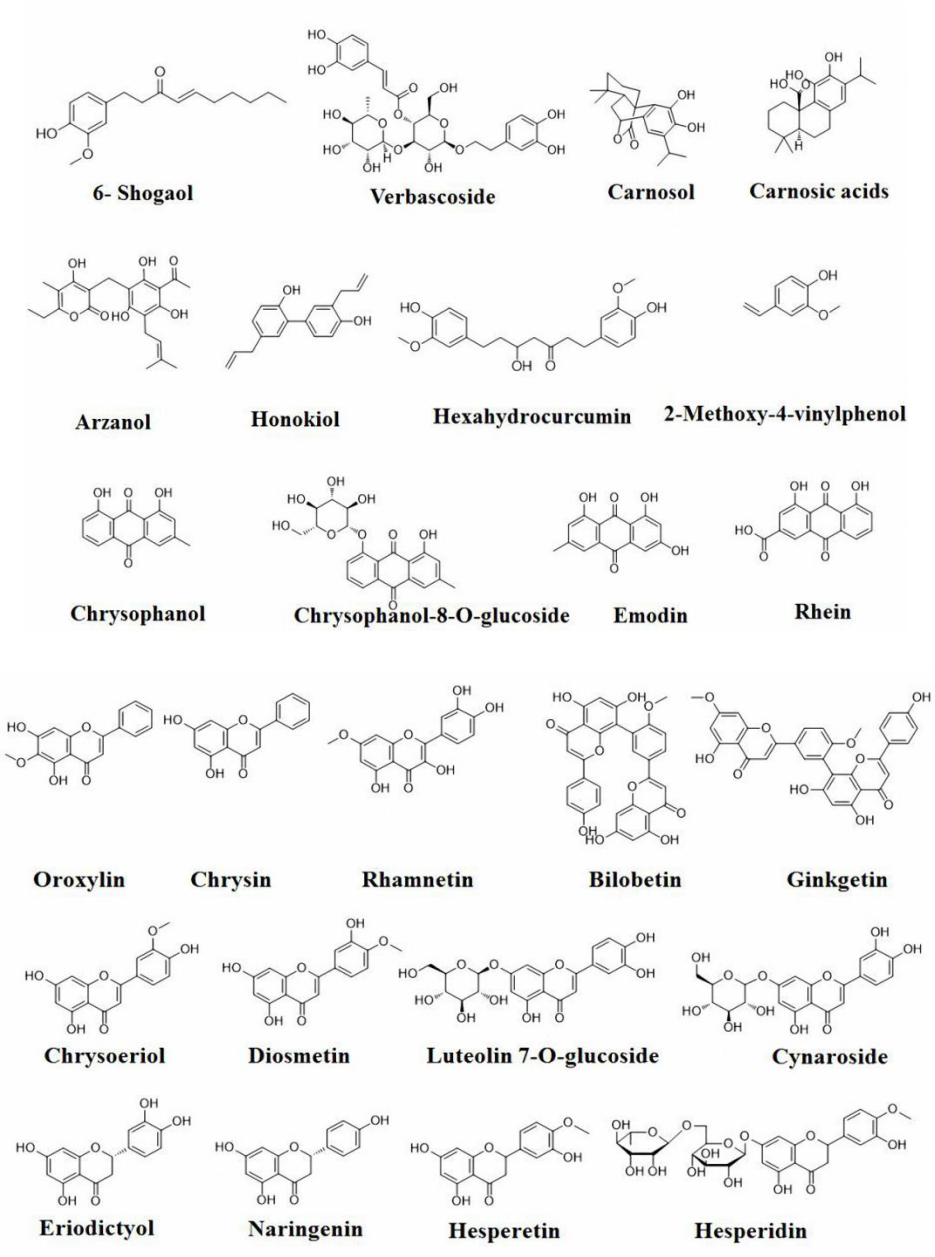


Figure 4. Chemical structures of active flavonoids (publications from 2011 to 2015).

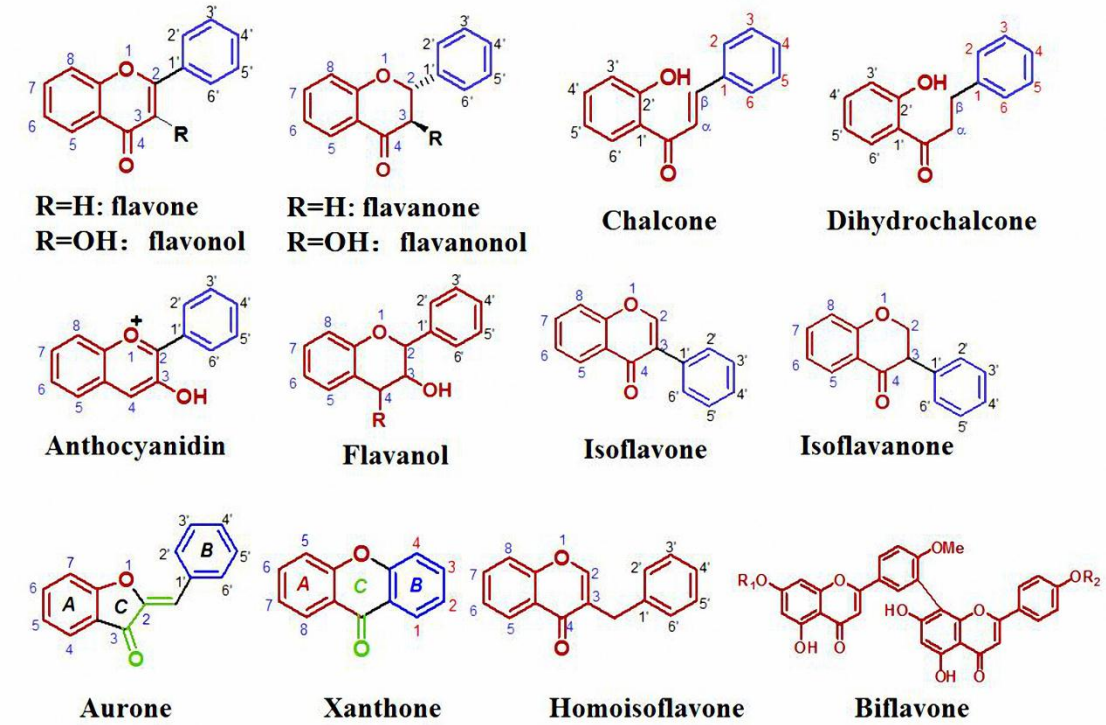
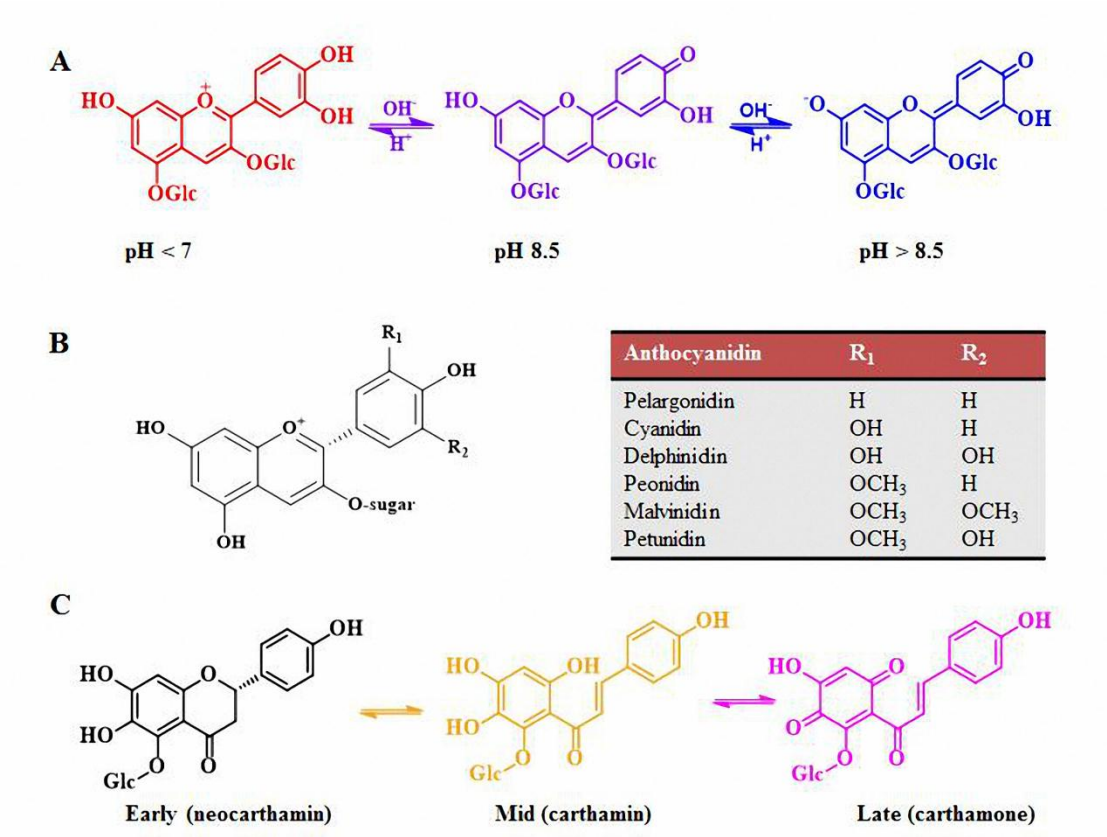


Figure 5. Chemical structures of flavonoid aglycones.



Anthocyanidin	R_1	R_2
Pelargonidin	H	H
Cyanidin	OH	H
Delphinidin	OH	OH
Peonidin	OCH_3	H
Malvinidin	OCH_3	OCH_3
Petunidin	OCH_3	OH

Figure 6. Chemical structures of anthocyanidin.

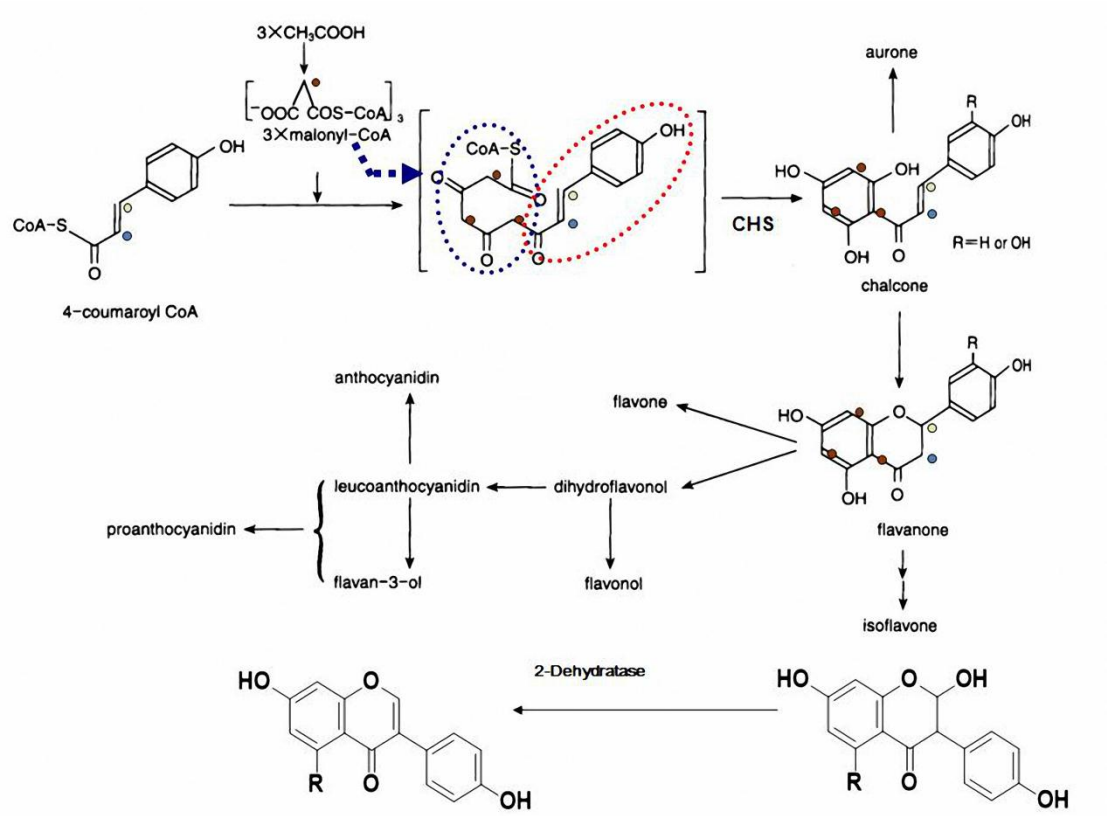


Figure 7. The pathway for isoflavone and anthocyanidin biosynthesis. First phenylalanine reacts with malonyl CoA to produce 4-hydroxycinnamoyl CoA. Under the catalytic control of chalcone synthase, 4-hydroxycinnamoyl CoA condenses with three molecules of malonyl CoA to form a chalcone. Chalcone isomerase closes the heterocyclic ring to form naringenin. The B-ring is moved from the C2-position to C3-position by isoflavone synthase. Isoflavone dehydratase removes water to generate the C2-C3 double bond in the heterocyclic ring (see Figure 1 for the numbering scheme).

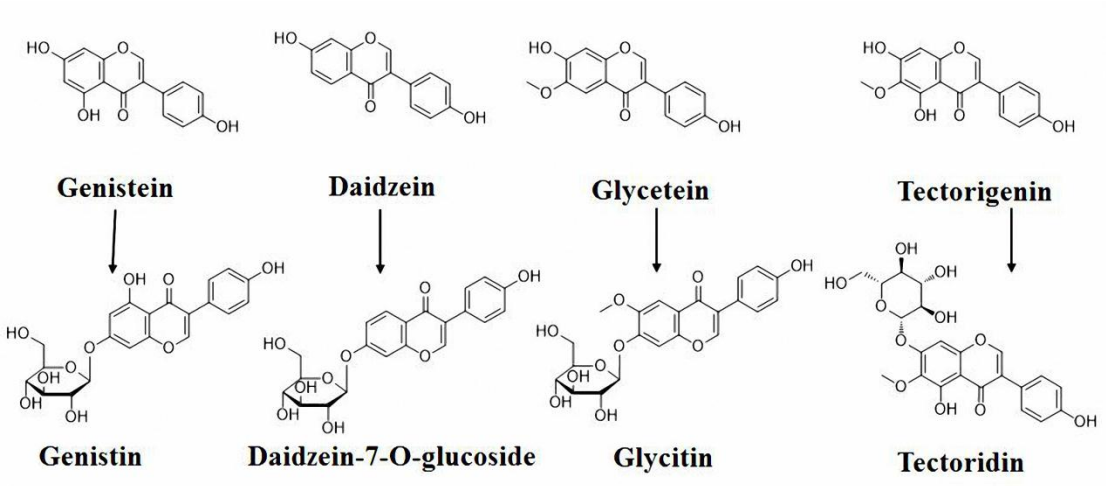


Figure 8. Molecular structures of isoflavones genistein, daidzein, glycetein, tectorigenin and and their glycoside.

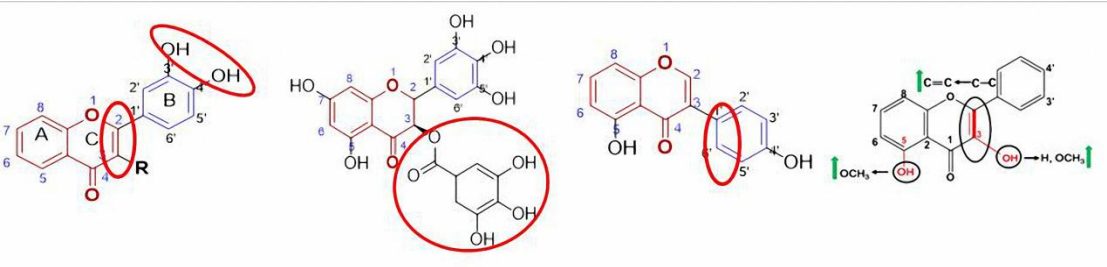


Figure 9. Effects of glycosylated and deglycosylated flavones on TNF- α and NF-kB activity. Adapt from Hostetler et al. (2012).

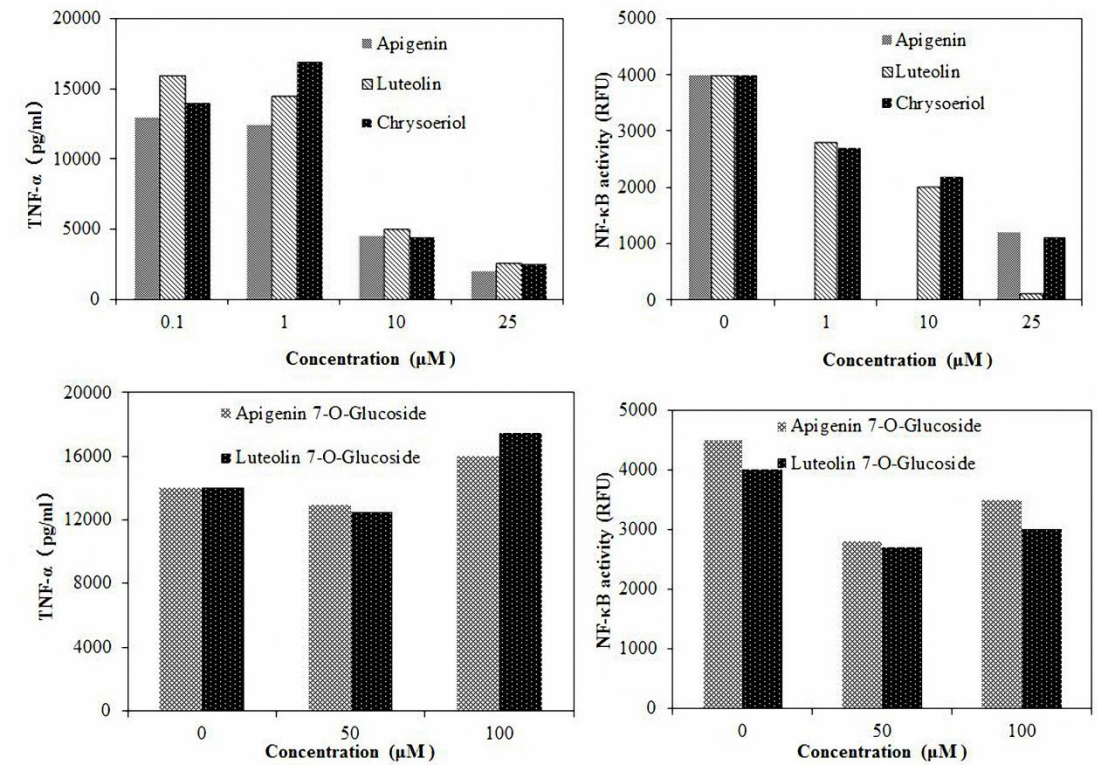


Figure 10. Relationship between flavonoid structure and anti-inflammatory effect. Important structural features of flavonoids for their activity are 4'-or 3'-, 4'-OH on the B ring and C2-C3double bond in the C ring in flavones and flavonols, 5-OH at the A ring of the isoflavones.