Flavonoids: Broad Spectrum Agents on Chronic Inflammation

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Abstract

Flavonoids are major plant constituents with numerous biological/pharmacological actions both *in vitro* and *in vivo*. Of these actions, their anti-inflammatory action is prominent. They can regulate transcription of many proinflammatory genes such as cyclooxygenase-2/inducible nitric oxide synthase and many cytokines/chemokines. Recent studies have demonstrated that certain flavonoid derivatives can affect pathways of inflammasome activation and autophagy. Certain flavonoids can also accelerate the resolution phase of inflammation, leading to avoiding chronic inflammatory stimuli. All these pharmacological actions with newly emerging activities render flavonoids to be potential therapeutics for chronic inflammatory disorders including arthritic inflammation, meta-inflammation, and inflammaging. Recent findings of flavonoids are summarized and future perspectives are presented in this review.

Key Words: Flavonoid, Chronic inflammation, Therapeutics, Inflammaging, Meta-inflammation

INTRODUCTION

Inflammation is the body defense mechanism against foreign insulting agents such as microbes. Some cellular components and metabolites can sometimes act as inflammatory insults to the body itself. Recent findings have suggested that high glucose level, obesity, aging, and body materials can produce autoantibodies to provoke inflammatory responses for a long period. Such chronic inflammation may lead to several disease states including gout, arthritis, vascular diseases, and late-stage cancers. Thus, long-term safe use of certain anti-inflammatory agents is necessary and agents that can inhibit these inflammatory conditions may have beneficial effect on the body. In this regard, plant-originated compounds might be potential candidates for this use.

Flavonoids (Fig. 1) are one of large entities of plant constituents. Some flavonoids possess significant anti-inflammatory activity both *in vitro* and *in vivo*. There have been many reviews of the anti-inflammatory flavonoids and their action mechanisms. Previously, we have claimed that certain flavonoids can exert their anti-inflammatory action largely by modulating the expression of proinflammatory molecules such as proinflammatory enzymes including cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and proinflammatory cytokines such as interleukin-1 (IL-1) and IL-6 (Kim *et al.*, 2004). In this respect, wogonin and its related molecules

have shown the most potent activity among the flavonoids examined (Kim *et al.*, 1999; Chi *et al.*, 2001, 2003). The new flavonoid derivatives with anti-inflammatory action have been continuously found and the findings are culminated (Lim *et al.*, 2009, 2011b). Among synthetic flavones, 8-pyridinyl flavonoid derivative can down-regulate the expression of COX-2 and iNOS (Lim *et al.*, 2011a).

Although certain flavonoids possess inhibitory effects on acute inflammatory responses both *in vitro* and *in vivo*, they are not expected to be desirable therapeutics against acute inflammation because currently used anti-inflammatory agents including nonsteroidal anti-inflammatory drugs (NSAIDs such as ibuprofen and indomethacin) or steroidal anti-inflammatory drugs (SAIDs such as prednisolone and dexamethasone) show pharmacological effectiveness in these clinical conditions. Besides, flavonoids show much lower anti-inflammatory potency than NSAIDs and SAIDs. However, flavonoids are potential therapeutics for chronic inflammatory conditions mainly because they can act on several chronic inflammatory conditions without showing serious side effects for a prolonged time whereas long-term use of NSAIDs or SAIDs is not tolerated mainly due to their serious complications. Thus, due to limitations of currently used anti-inflammatory agents, flavonoids have clear advantages as new anti-inflammatory agents targeting chronic conditions.

Here, we summarize findings of anti-inflammatory flavo-

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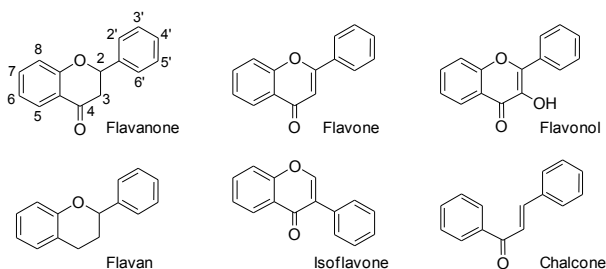
Fig. 1. Some basic chemical structures of flavonoids.

noids for chronic inflammatory disease conditions including arthritis, metabolic inflammation, and age-related inflammation. Some significant and important recent findings related to anti-inflammatory flavonoid researches since 2011 are also summarized and future perspectives are discussed.

EFFECTS OF FLAVONOIDS ON ANIMAL MODELS OF ARTHRITIS (JOINT INFLAMMATION)

Human joint inflammation is caused by various endogenous and exogenous insults. Examples include repeated pressure to the cartilage, cold weather, and joint infection by microbes. Several inflammatory disorders can also provoke joint inflammation. Among them, rheumatoid arthritis (RA) and osteoarthritis (OA) are the most important. In these disease processes, continuous inflammatory stimulation provides deleterious effects on cells in joint space (Goldring and Otero, 2011; Choy, 2012). Synovial fibroblasts are important cells specially involved in RA. Activated synovial fibroblasts and macrophages in acute phases can be effectively controlled by oral and/or topical application of NSAIDs and SAIDs (Quan *et al*., 2008). In RA, many immunological parameters can lead to symptoms (edema, fever, pain, and cartilage breakdown) in various joints of the body. Neutrophils and lymphocytes in the synovial space are also involved (Fox *et al*., 2010). Although many derivatives positively affect acute inflammation in various animal models, only few flavonoids have been reported to be able to inhibit inflammatory responses and symptoms in animal models of RA. For instance, quercetin, genistein, apigenin, and kaempferol reduced arthritic inflammation in RA models such as collagen-induced arthritis (Li *et al*., 2013, 2016c; Haleagrahara *et al*., 2017; Pan *et al*., 2018). These inhibitory actions of flavonoids against animal models of RA might be attributed to their modulatory effects on neutrophils, macrophages, and lymphocytes. Especially, quercetin could lower neutrophil recruitment to the joint in zymosan-induced arthritis (Guazelli *et al*., 2018). Impacts of flavonoids on these inflammatory cells have been well summarized (Middleton, 1998). Nonetheless, it is necessary to emphasize that flavonoids can differentially affect functions of macrophage types M1 and M2 (Saqib *et al*., 2018; Tong *et al*., 2018). This finding is important in that the switch of macrophage phenotype determines either pro- or anti-inflammatory process in inflammatory diseases. So far, there are few reports about protective effects by direct regulation of flavonoids focusing on macrophage polarization in arthritis model. However, it is reasonable that flavonoids might also have potential for treating arthritic inflammation due to

roles of flavonoids such as quercetin, apigenin, and epigallo-catechin gallate (EGCG) as potent modulators of macrophage phenotype (Feng *et al*., 2016; Kim *et al*., 2016a; Machova Urdzikova *et al*., 2017). Effects of flavonoids on macrophage phenotype switching are described further in the section of inflammatory resolution. All these results indicate that some flavonoids can inhibit several aspects of animal models of RA. However, it remains unclear whether flavonoids can really alleviate acute and/or chronic inflammatory responses clinically in RA. On the other hand, certain flavonoids might be able to affect or prevent cartilage degradation through long-term use.

Early phase of OA is characterized by pain and cartilage breakdown. These symptoms progressively become severe upon aging. In the lesion, inflammation-related cells like neutrophils and macrophages are rarely recruited. Rather, some chondrocytes are dead by apoptosis and elevated levels of cartilage degrading enzymes are expressed (Goldring and Otero, 2011). Meanwhile, osteoarthritic joints would experience edema and swollen lesion later, leading to the acceleration of joint breakdown. So far, to prevent or slow down the progression of osteoarthritis, anti-inflammatory treatment using IL-1 or TNF-α specific antibodies or receptor antagonists and strategies to interfere with cartilage breakdown have been developed (Cohen *et al*., 2011; Wang, 2018; Wan *et al*., 2018). Thus, it is notable that some flavonoids not only exert anti-inflammatory activity as mentioned above, but also possess inhibitory action on the expression of cartilage breakdown enzymes such as matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS).

Chondrocytes residing in cartilage are important cells. They are responsible for degrading extracellular matrix (ECM) in joint space, especially under conditions of OA (Goldring, 2000). They can synthesize ECM materials such as collagen type II and aggrecan. They can also synthesize and secrete ECM metalloproteinases such as collagenases and aggrecanases that are proteolytic enzymes. MMPs are proteinases that can hydrolyze extracellular matrix proteins including collagens and elastins. Among 24 MMPs found in human, MMP-1, -3, and -13 are collagenases, of which MMP-13 is the most important one in degrading cartilage collagens in normal ECM turnover process and/or in diseased-state such as OA (Wang *et al*., 2013). On the other hand, MMP-1 is major collagenase in the skin. It also participates in the turnover process of ECM materials of the cartilage. ADAMTS-4 and -5 are also pivotal ECM degrading enzymes. They are involved in normal turnover process in ECM generation, although they are somewhat induced in disease conditions (Dancevic and McCulloch, 2014). Therefore, inhibitors and/or down-regulators of these enzymes might have beneficial effects against cartilage breakdown, a final step of OA. Actually, various MMPs and ADAMTS inhibitors have been developed and some of them are under clinical trial.

It is important to mention that certain flavonoids that can inhibit enzymatic activities of MMPs and/or suppress induction of several important MMPs involved in cartilage degradation have been found. Delphinidin (anthocyanin), flavonol derivatives (including quercetin, kaempferol, and hyperoside), and catechins with a galloyl moiety inhibit activities of gelatinases (MMP-2 and -9) and neutrophil elastase (MMP-12) (Melzig *et al*., 2001; Sartor *et al*., 2002; Im *et al*., 2014). Green tea polyphenols including EGCG, theaflavin, and proanthocyanidins

also inhibit membrane-type 1 matrix metalloproteinase (MT1-MMP) (Oku et al., 2003; Zgheib et al., 2013; Djerir et al., 2018). On the other hand, when ultraviolet (UV)-irradiated human skin, UV-irradiated human dermal fibroblasts (HDFs), human vascular endothelial cells, and human synovial fibroblasts are treated with flavonoids, some flavonoids such as genistein, baicalein, quercetin, and nobiletin down-regulated MMP-1 expression (Kang et al., 2003; Lin et al., 2003; Sung et al., 2012; Yi et al., 2012; Zhang et al., 2014). We have also found that some naturally-occurring flavonoids can inhibit MMP-1 expression in skin fibroblasts and interrupt c-Jun N-terminal kinase (JNK)/c-Jun activation (Lim and Kim, 2007). It was also revealed that certain flavonoid derivatives inhibited MMP-13 induction in chondrocytes (Lim et al., 2011b). These reports have demonstrated that quercetin and kaempferol suppress MMP-1 expression via inhibition of mitogen-activated protein kinase (MAPK) and activator protein-1 (AP-1) activation in human skin fibroblasts without inhibiting MMP-13 expression in SW1353 cells, a chondrocyte cell line. Flavones such as apigenin and wogonin could decrease MMP-1 expression without affecting MAPK pathway in skin fibroblasts. Especially, the inhibitory effect of apigenin and 2',3',5,7-tetrahydroxyflavone on MMP-13 expression in chondrocytes was found to be mediated by the inhibition of c-Fos/AP-1 and janus kinase 2 (JAK2)/signal transducers and activators of transcription 1/2 (STAT1/2) pathway. As shown in these results, signaling pathways related to the expression of MMP-1 and MMP-13 are differentially regulated depending on types of flavonoid and cells or tissues. In addition, some flavonoids can inhibit AD-AMTS-4 and -5 known to be key enzymes for aggrecan degradation during osteoarthritis (Majumdar et al., 2007). Recent studies have demonstrated that flavonoids such as silibinin, chrysin, baicalin, and wogonin suppressed MMP-1 and -13, but also suppressed ADAMTS-4 and/or -5 through signal-

ing molecules such as phosphatidylinositol 3 kinase/protein kinase B (PI3K/Akt), nuclear transcription factor-κB (NF-κB), and nuclear factor erythroid-derived 2-related factor 2 (Nrf2) in animal OA model (Chen et al., 2017; Khan et al., 2017; Zheng et al., 2017a, 2017b). Although clinical data are currently unavailable, it is certain that some flavonoids can act on animal models of joint inflammation. They might be especially protective against cartilage destruction probably through downregulation of MMP expression (Fig. 2). This point should be verified further in the future.

EFFECTS OF FLAVONOIDS ON AGING-RELATED INFLAMMATION (INFLAMMAGING)

Cellular aging process comprises various aspects of cellular metabolism. Cells become larger and eventually stop their division known as cellular senescence that prevents cancer formation in general. Thus, aging process is considered to provide some beneficial effects. However, recent studies have found that aged cells synthesize and secrete some inflammation-related molecules called senescence-associated secretory phenotype (SASP), including inflammatory cytokines such as IL-6, IL-8, IL-1, and MMPs (Tchkonia et al., 2013). Serum IL-6 level in elderly humans has been found to be significantly elevated regardless of diseases (Bruunsgaard et al., 2001; Ferrucci et al., 2005). These secreted molecules affect nearby cells to provoke inflammatory responses, eventually producing aging-related chronic inflammation called inflammaging, one type of sterile persistent inflammation. Thus, long-term stimulation by SASP molecules induces various metabolic changes including cardiovascular changes (Franceschi and Campisi, 2014). Sometimes they lead to late-stage cancer (Campisi, 2013). Thus, blocking SASP production may be ef-
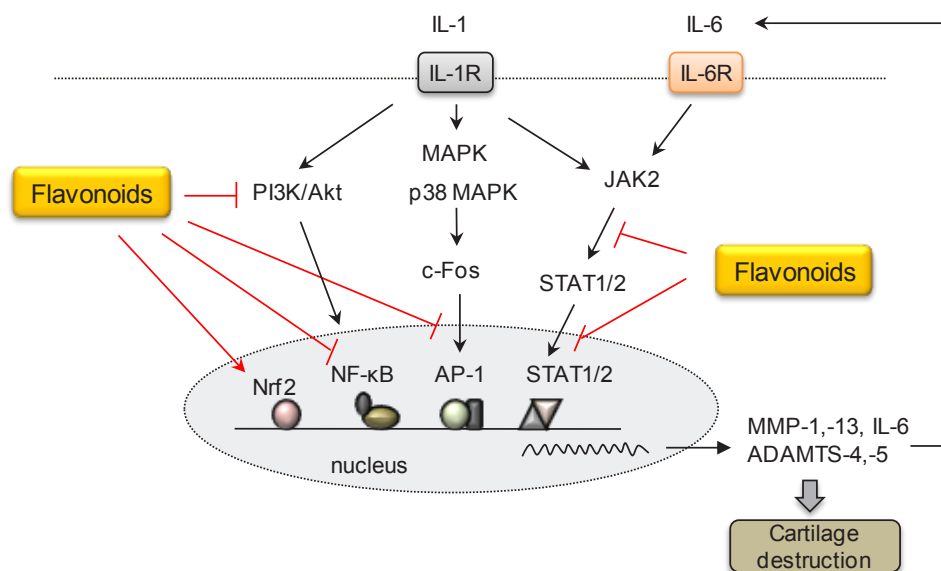
Fig. 2. Effects of flavonoids on the expression of MMP and ADAMTS in osteoarthritis. MMP and ADAMTS are enzymes that play crucial roles in ECM degradation in osteoarthritis progression. Flavonoids such as apigenin and 2',3',5,7-tetrahydroxyflavone inhibit MMP-13 expression via c-Fos/AP-1 and JAK2/STAT1/2 pathway in IL-1β-treated chondrocyte cell line. In animal OA model, flavonoids such as silibinin, chrysin, baicalin, and wogonin show protective effects by downregulation of ADAMTS-4 and/or -5 expression through PI3K/Akt, NF-κB and/or Nrf2 signaling pathways. IL-1R, IL-1 receptor; IL-6R, IL-6 receptor.

fective for achieving healthy aging. Many laboratories have been searching for agents to prevent the aging process itself. However, in our opinion, stopping cellular senescence may have other harmful effects on the body. Blocking cells to go into senescence cells means that they still have proliferating capacity, although they are old. This may deleteriously lead to cancer formation. In this respect, inhibition of SASP formation without affecting aging capacity (inhibition of inflammaging) seems to be a safe new target for healthy aging. To prove the beneficial effect of flavonoids on senescence and SASP production, we have evaluated several types of flavonoid derivatives, and found that apigenin and specific synthetic flavone can strongly inhibit SASP production without changing aging markers in both *in vitro* and *in vivo* models (Lim *et al*., 2015). Blocking SASP production by apigenin has been shown to be related to the interruption of NF-κB p65 activation and interleukin-1 receptor-associated kinase 1 (IRAK1)/IκBα signaling pathway in bleomycin-induced senescence of BJ fibroblasts (Lim *et al*., 2015). Moreover, apigenin strongly reduced gene and protein expression of IκBζ transcription factor both *in vitro* and *in vivo*. It has been previously shown that IκBζ is closely associated with SASP induction such as IL-6 and IL-8 (Alexander *et al*., 2013). Transcription factors such as NF-κB and CCAAT/enhancer-binding protein beta (C/EBPβ) are known as signaling molecules regulating SASP production (Salminen *et al*., 2012; Huggins *et al*., 2013). Flavonoids such as baicalin and kaempferol inhibited the production of some cytokines through NF-κB signaling in aged rat (Kim *et al*., 2010; Lim *et al*., 2012). Signaling molecules such as protein kinase D1, p38 MAPK, MAPK-activated protein kinase-2 (MK2), and mixed-lineage leukemia 1 (MLL1) have been suggested to play essential roles in producing SASP molecules (Alimbetov *et al*., 2016; Capell *et al*., 2016; Su *et al*., 2018). Besides, several reports have demonstrated the regulation of SASP factors by some microRNAs (Panda *et al*., 2017).

In case of dietary flavonoids, cohort studies have suggested that flavonoid intake is inversely associated with age-related diseases such as cardiovascular disease (CVD), neurodegeneration, and type 2 diabetes (Root *et al*., 2015; Grosso *et al*., 2017; Kim and Je, 2017; Lefèvre-Arbogast *et al*., 2018; Zhou *et al*., 2018). In studies investigating the underlying mechanism for this phenomena, administration of fisetin and rutin

in animal models has shown protective activity by preventing increased production of IL-1β and tumor necrosis factor-α (TNF-α) in age-related disorders such as neurodegeneration and metabolic dysfunction (Li *et al*., 2016b; Singh *et al*., 2018). Uptake of luteolin, baicalin, genistein, and kaempferol also lowered the elevated level of inflammatory cytokines such as IL-1β and IL-6 or NF-κB activation in aged animal model (Kim *et al*., 2010, 2011; Lim *et al*., 2012; Burton *et al*., 2016).

Inflammasome activation is also associated with the aging process. Many damage-associated molecular patterns (DAMPs) such as uric acid and cholesterol crystal are increased with age, leading to chronic low-grade inflammation following inflammasome activation (Huang *et al*., 2015). Aging tissue has high degree of NF-κB activation. Aging can stimulate inflammasome activation to produce inflammatory cytokines such as IL-1β and IL-18 (Song *et al*., 2016). With SASP, these cytokines may have more impacts on cells to accelerate the aging process. Expression of inflammasome gene modules including IL-1β is positively associated with human aging, especially in those aged over 85 years (Furman *et al*., 2017). For neutralization of IL-1β, treatment with IL-1β antibody for patients with myocardial infarction and low-grade inflammation reduces cardiovascular mortality (Ridker *et al*., 2018). Recent studies have demonstrated the role of inflammasome in metabolic disease such as human diabetes that is more likely to develop with age (Bauernfeind *et al*., 2016; Cordero *et al*., 2018). With respect to bacterial infection during aging, lipopolysaccharide (LPS) treatment in aged rat can lead to long-lasting neuroinflammation through NF-κB activation and excessive IL-1β release in the hippocampus (Fu *et al*., 2014). In the liver of aged rats, the expression of Nod-like receptor protein 3 (NLRP3)-related components such as NLRP3, apoptosis-associated speck-like protein containing a C-terminal caspase recruitment domain (ASC), caspase-1, and IL-1β are apparently increased than those in young rats during LPS-induced endotoxemia (Chung *et al*., 2015). Increased level of IL-1β in adipose tissue could induce age-dependent overproduction of IL-6 through autocrine/paracrine action (Starr *et al*., 2015). In addition, due to elevation of NLRP3 inflammasome at basal level with age, it has been demonstrated that specific bacterial clearance does not properly work (Krone *et al*., 2013).

To develop a therapeutic tool to target inflammaging, it is
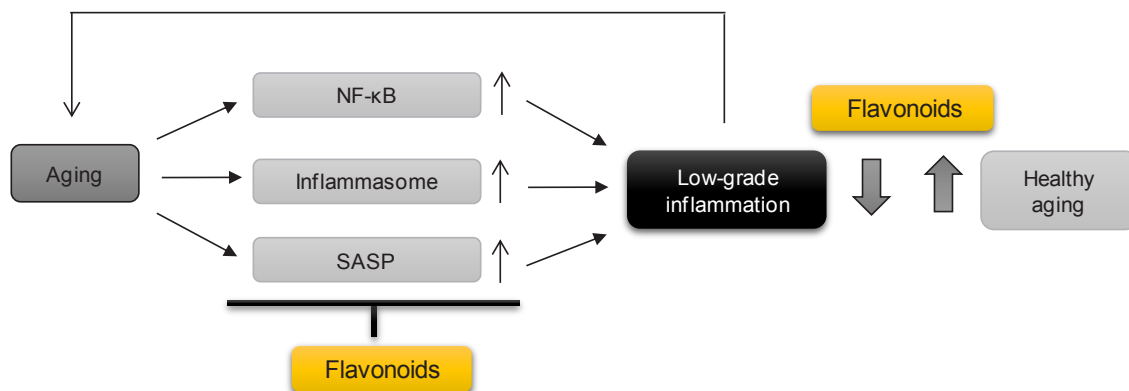
Fig. 3. Effects of flavonoids on inflammaging. Cellular aging causes low-grade chronic inflammation, called inflammaging. Some flavonoids have potential as therapeutic candidates for healthy aging by modulating the markers of aging-associated inflammation such as NF-κB activation, inflammasome activation and SASP production.

necessary to find an inflammasome inhibitor that has the potential to suppress the expression of inflammasome components or directly block inflammasome activation itself. Since flavonoids have effects on SASP production and inflammasome activation associated with aging (Fig. 3), dietary uptake of flavonoids or flavonoid-rich food and vegetables could help reduce the level of age-related inflammation, ultimately leading to healthy aging.

EFFECTS OF FLAVONOIDS ON OBESITY-ASSOCIATED INFLAMMATION (METABOLIC INFLAMMATION, META-INFLAMMATION)

Obesity causes chronic and persistent inflammation in adipose tissue which is closely linked to the development of metabolic disease such as insulin resistance, type 2 diabetes, and cancer (Divella *et al.*, 2016; Saltiel and Olefsky, 2017). Adipocytes are known to secrete chemokines such as monocyte chemoattractant protein-1 (MCP-1) that can induce macrophage infiltration into adipose tissue. Adipose tissue macrophages play a crucial role in obesity-associated inflammation and insulin resistance (Amano *et al.*, 2014; Engin, 2017). Infiltrated macrophage is activated to M1 phenotype that secretes pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 to induce chronic inflammation. These cytokines can lead to the development of insulin resistance and apoptosis of pancreatic beta-cells (Appari *et al.*, 2018). It is now clear that obesity produces inflammatory environment to the body that can lead to chronic inflammation and meta-inflammation, thus having deleterious effects on the body.

So far, many reports have demonstrated the anti-obesity activity of flavonoids by modulating the production of inflammatory molecules via affecting several cellular signaling pathways. In particular, there have been several reports concerning quercetin in obesity-associated inflammation. Quercetin inhibited the inflammatory response of macrophages via activation of adenosine monophosphate-activated protein kinase (AMPK) a1 phosphorylation and sirtuin 1 (SIRT1) expression (Dong *et al.*, 2014). Quercetin also reduced obesity-induced hypothalamic inflammation accompanied by heme oxygenase (HO)-1 induction in microglia (Yang *et al.*, 2017). The effect of quercetin on HO-1 induction is correlated with macrophage phenotype switching effect in hepatic inflammation caused by obesity (Kim *et al.*, 2016a). These effects of quercetin have been proven *in vivo* by the finding that supplementation with quercetin into mice for 18 weeks reduced the number of macrophages in adipose tissue (Kobori *et al.*, 2016). Butein chalcone also induced HO-1 expression via p38 MAPK/Nrf2 pathway in adipocytes (Wang *et al.*, 2017b).

Besides, EGCG reduced macrophage infiltration and insulin resistance in high-fat diet (HFD) animal model and suppressed toll-like receptor 4 (TLR4) expression which is strongly associated with obesity-induced inflammation due to the first trigger-action (Bao *et al.*, 2014; Cao *et al.*, 2014; Kumazoe *et al.*, 2017). Naringenin also inhibits macrophage infiltration involved in JNK pathway (Yoshida *et al.*, 2014). A recent study has shown that apigenin attenuated metabolic inflammation via peroxisome proliferator-activated receptor (PPARγ) activation and lowered malondialdehyde, IL-1β, and IL-6 colonic levels in HFD mouse model (Feng *et al.*, 2016; Gentile *et al.*, 2018). Specific chalcone derivatives prevented HFD-induced

heart and kidney injury via MAPK and NF-κB signaling pathway (Fang *et al.*, 2015; Chen *et al.*, 2018). In addition, there have been several reports on anti-obesity effects of flavonoids such as isoflavone daidzein (Sakamoto *et al.*, 2016), luteolin (Xu *et al.*, 2014), chrysin (Feng *et al.*, 2014b), and rutin (Gao *et al.*, 2013) by suppressing inflammation.

Cohort studies on flavonoid intake and obesity have been continuously carried out (Bertoia *et al.*, 2016; Marranzano *et al.*, 2018). Considering with the anti-inflammatory effect of flavonoids, a recent cohort study has also shown that flavonoid intake is inversely associated with body mass index and level of C-reactive protein which is produced in response to inflammation (Vernarelli and Lambert, 2017). All these studies suggest that flavonoids can reduce obesity and obesity-related chronic inflammation.

EFFECTS OF FLAVONOIDS ON INFLAMMATORY RESOLUTION

To finish an inflammatory process in the body, inflammatory resolution should properly work. Inflammatory resolution is tightly regulated by cellular pathways involving many signaling molecules and factors in the pathological progress of inflammatory diseases. During resolution, not only pro-inflammatory mediators are negatively regulated, but also immune cell influx are stopped by the action of lipid mediators such as lipoxin A4 and resolvin E1 followed by clearance of recruited neutrophils from inflamed sites in the way of apoptosis or necrosis (Schett and Neurath, 2018). However, dysregulation of acute inflammatory resolution can lead to chronic inflammation in which the balance between innate and adaptive immunity is inadequately controlled (Fullerton and Gilroy, 2016). In particular, during inflammatory resolution, it has been demonstrated that the population of macrophage phenotype can specifically determine either deleterious or protective role depending on the type and state of inflammatory diseases (Anders and Ryu, 2011; Liu *et al.*, 2014; Parisi *et al.*, 2018).

Flavonoids are known to regulate macrophage polarization at post-resolution and down-regulate pro-inflammatory signals at initiation of resolution. Importantly, it has been found that chrysin induced anti-inflammatory M2 phenotype and decreased M1 phenotype in macrophages (Feng *et al.*, 2014b). It has also been demonstrated that pentamethoxyflavanone inhibited M1 phenotype but increased M2 phenotype macrophages (Feng *et al.*, 2014a). In line with these observations, quercetin can inhibit hepatic M1 macrophage and gene expression of M1-related inflammatory cytokines in carbon tetrachloride-induced liver fibrosis and obesity-induced hepatic inflammation (Dong *et al.*, 2014; Kim *et al.*, 2016a; Li *et al.*, 2018). Apigenin reversed M1 macrophage into M2 via activation of PPARγ in HFD and ob/ob mice (Feng *et al.*, 2016). Rutin also induced microglial polarization to M2 phenotype, suggesting its potential to possibly treat neurodegenerative disease (Bispo da Silva *et al.*, 2017). Baicalin and naringenin reduced inflammatory symptom caused by M1 to M2 macrophage polarization in inflammatory bowel disease and atopic dermatitis, respectively (Karuppagounder *et al.*, 2016; Zhu *et al.*, 2016).

Therefore, flavonoids can affect all phases of inflammatory responses. Since regulation of inflammatory resolution is important in chronic inflammatory disorders, it is suggested that

flavonoids are promising agents that can alleviate symptoms of chronic inflammation.

NEW ANTI-INFLAMMATORY CELLULAR MECHANISMS OF FLAVONOIDS
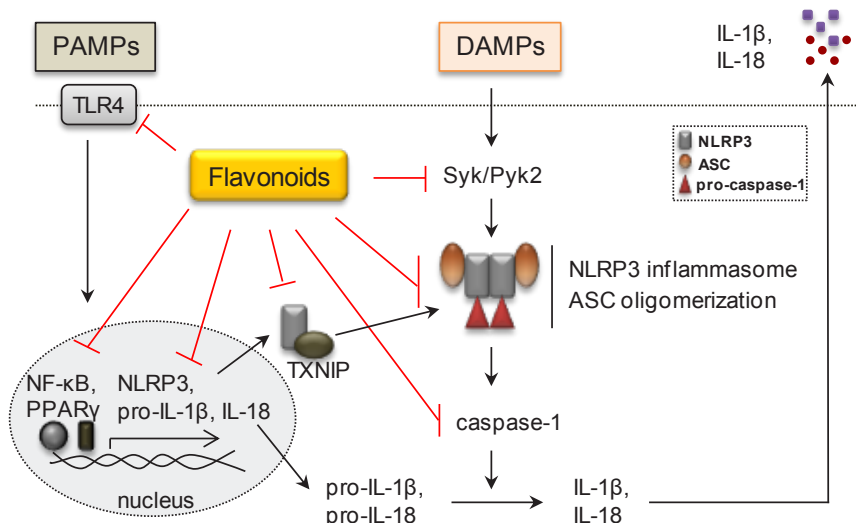
Effects on TLR and inflammasome pathways

For inflammasome activation as first-line defense of innate immunity, a priming step via TLR is a prerequisite for subsequent activation step, leading to the production of pro-forms of IL-1β and IL-18 and NLRP3 protein through NF-κB activation (He *et al*., 2016b). Inhibitory effects of flavonoids such as anthocyanin, luteolin, hyperin, and alpinetin on inflammasome through TLR4/NF-κB/NLRP3 pathway have been demonstrated in several reports (Chunzhi *et al*., 2016; He *et al*., 2016a; Zhang *et al*., 2017b; Cui *et al*., 2018). Until now, many flavonoids have been found to be able to inhibit the NLRP3 inflammasome pathway. Studies on flavonoids having inhibitory effects on the inflammasome have been mainly focused on inhibition of the expression of NLRP3 inflammasome-related components such as IL-1β, IL-18, NLRP3, and caspase-1.

Quercetin inhibited kidney injury in rats via regulation of NLRP3 inflammasome (Wang *et al*., 2012). In case of protective effect of flavonoids on gout arthritis, effects of quercetin, hesperidin methylchalcone, EGCG, and morin in relation to NLRP3 inflammasome have been demonstrated in several animal models (Dhanasekar and Rasool, 2016; Jhang *et al*., 2016; Ruiz-Miyazawa *et al*., 2017, 2018). Luteolin as a caspase-1 enzyme inhibitor has shown cardioprotective effect by reducing the expression of NLRP3 and ASC protein both in *in vitro* and *in vivo* myocardial ischemia/reperfusion model (White *et al*., 2012; Zhang *et al*., 2017b). Luteoloside downregulated protein expression levels of NLRP3, matured IL-1β, and caspase-1 in hepatocellular carcinoma cell line (Fan *et al*., 2014). Rutin and morin also possess inhibitory effects on

NLRP3 inflammasome in several animal models (Aruna *et al*., 2014; Dhanasekar and Rasool, 2016; Wang *et al*., 2017a).

It is evident that several types of flavonoids can inhibit NLRP3 inflammasome by decreasing the expression of inflammasome components and/or blocking inflammasome assembly such as ASC oligomerization. For instance, EGCG abundant in tea can inhibit NLRP3 inflammasome conjugation with thioredoxin-interacting protein (TXNIP) in THP-1 cells and ameliorate peritoneal inflammation by inhibiting NLRP3 expression and IL-1β release in monosodium urate (MSU) crystal-treated mice (Jhang *et al*., 2016). Quercetin can inhibit the expression of NLRP3 and IL-1β and caspase-1 activity in human colonic epithelial cells. It also has inhibitory effects on NLRP3 and absent in melanoma 2 (AIM2) inflammasome by preventing ASC oligomerization in both *in vitro* and *in vivo* mouse vasculitis model (Domiciano *et al*., 2017; Xue *et al*., 2017). Apigenin can reduce IL-1β and IL-18 release and NLRP3 expression in chronic unpredictable mild stress (CUMS)-induced rat brain (Li *et al*., 2016a). Isoliquiritigenin, a chalcone derivative, has shown similar dual activity in adipose tissue inflammation (Honda *et al*., 2014).

As noted above, some flavonoid derivatives can inhibit IL-1β production. However, most of them only reduce IL-1β production via inhibition of pro-IL-1β expression. Only a few flavonoids such as quercetin could reduce NLRP3 activation and ASC oligomerization. To clearly establish their pharmacological action on NLRP3 activation, many flavonoids have been further examined. In our previous study, several flavonoid derivatives have been found to be able to inhibit IL-1β production in MSU-treated THP-1 cells (Lim *et al*., 2018). Especially, apigenin, kaempferol, and 3',4'-dichloroflavone reduced IL-1β production by inhibition of ASC oligomerization regardless of intracellular ASC level. The inhibitory effect of apigenin on activation of NLRP3 inflammasome has been proven to be attributed to spleen tyrosine kinase/protein tyrosine kinase 2 (Syk/Pyk2) pathway (Fig. 4). Furthermore, apigenin administration

Fig. 4. Effects of flavonoids on signaling pathway of NLRP3 inflammasome activation. Many flavonoids possess anti-inflammatory activities by interrupting various signaling stages of NLRP3 inflammasome pathway both *in vitro* and *in vivo*. They inhibit the expression of NLRP3 inflammasome-related components such as IL-1β, IL-18, NLRP3, and caspase-1 and/or block inflammasome assembly which are mediated through signaling molecules such as TLR4/NF-κB/NLRP3, PPARγ, TXNIP and Syk/Pyk2, etc.

can inhibit the number of infiltrated inflammatory cells in MSU-induced peritonitis in mice (Lim *et al*., 2018). All these findings clearly indicate that some flavonoids can interrupt inflammasome production that could contribute to the anti-inflammatory activity of certain flavonoids both *in vitro* and *in vivo*.

Recently, besides canonical inflammasome pathways, the importance of noncanonical pathways has been emerged in inflammasome activation accompanied by components such as caspase-8, -11, and P2X7 receptor (P2X7R) (Kayagaki *et al*., 2011; Gurung *et al*., 2014; Ousingsawat *et al*., 2018). It has been shown that apigenin supplementation can inhibit both caspase-1 and caspase-11 in chronic ulcerative colitis model (Márquez-Flores *et al*., 2016). However, in another report, the protective effect of apigenin against acute colitis has been suggested to be mediated by NLRP6 signaling pathway independent of caspase 1, 11, or ASC (Radulovic *et al*., 2018). Dihydroquercetin has hepatoprotective activity through P2X7R/NLRP3 inflammasome pathway (Zhang *et al*., 2018). Thus, whether flavonoids targeting inflammasome components in canonical pathway can also affect these components involved in noncanonical inflammasome pathways should be further studied.

Effects on autophagy

Autophagy maintains internal homeostasis by clearing damaged organelles, proteins, and intracellular pathogens through lysosomal degradative pathway (Glick *et al*., 2010). Impairment of autophagy can lead to many diseases such as cancer, cardiovascular disease, infectious disease, and neurodegenerative disease (Jiang and Mizushima, 2014). Due to the protective role of autophagy in the pathophysiology, autophagy modulation has been focused as an important target to regulate these diseases (Rubinsztein *et al*., 2012).

Signaling molecules (such as mammalian target of rapamycin (mTOR), AMPK, unc-51 like autophagy activating kinase 1/2 (ULK1/2), and LC3) and multiple transcription factors are involved in autophagy activation (Levy *et al*., 2017). Many reports have proven that flavonoids with antioxidant activity as one of their detoxification ability can stimulate autophagy through mitochondria-endoplasmic reticulum and proteasome both *in vitro* and *in vivo* (Hasima and Ozpolat, 2014). In various cancer cell lines, flavonoids such as quercetin, apigenin, silibinin, and EGCG can increase the expression of Beclin-1, LC3-II, and several types of autophagy-related (ATG) (Jiang *et al*., 2015; Hu *et al*., 2015; Wang *et al*., 2016; Yang *et al*., 2018). However, depending on the type or stage of cancer cell, autophagy can either promote or suppress cancer cells (Gewirtz, 2014). Thus, cancer therapy targeting autophagy pathway using flavonoids requires accurate regulation under a precise understanding of autophagy.

It is important to note that some flavonoids can reduce abnormal protein aggregates such as β-amyloid peptides and hyperphosphorylated tau protein through autophagy pathway in Alzheimer's disease. Quercetin prevented β-amyloid aggregation by activating macroautophagy in *Caenorhabditis elegans* (Regitz *et al*., 2014). It has been shown that fisetin degraded phosphorylated tau through autophagy activation mediated by transcription factors such as transcription factor EB (TFEB) and Nrf2 (Kim *et al*., 2016b). EGCG also decreased phospho-tau protein by increasing mRNA expression of autophagy adapter proteins in rat primary neuron culture (Chesser *et al*., 2016). For Parkinson's disease (PD), treatment with baicalin

and quercetin augments autophagic functions and leads to prevention against rotenone-induced neurotoxicity in an *in vivo* PD model (El-Horany *et al*., 2016; Kuang *et al*., 2017).

Flavonoids also have potential for cardioprotective therapy by activating cardiac autophagy. For instance, nobiletin has shown myocardial protective effect by restoring autophagy flux after acute myocardial infarction model in rats (Wu *et al*., 2017). Apigenin can relieve LPS-induced myocardial injury through modulation of autophagic components such as lysosomal-associated membrane protein 1 (LAMP1), ATG5, p62, and TFEB (Li *et al*., 2017). Due to positive effects of vitexin, rutin, EGCG, and luteolin on autophagy regulation, therapeutic potential of flavonoids against cardiovascular disease have also been suggested (Hu *et al*., 2016; Xuan and Jian, 2016; Ma *et al*., 2017; Zhang *et al*., 2017a). In addition, flavonoids such as naringenin, baicalin, EGCG, and quercetin have protective effects against bacteria or virus infection by promoting autophagy activation (Tsai *et al*., 2017; Xue *et al*., 2017; Lin *et al*., 2018; Oo *et al*., 2018). All these newly found effects suggest that flavonoids could be promising candidates based on their ability to modulate autophagy for the treatment of degenerative diseases associated with defective autophagy.

LIMITATION OF FLAVONOIDS AS THERAPEUTIC AGENTS: BIOAVAILABILITY AND METABOLISM

As mentioned above, various flavonoid derivatives possess anti-inflammatory activity in a variety of animal models of inflammation. Nonetheless, it is apparent that flavonoids in general do not show strong effects by oral administration enough for a clinical trial. As reported by many researchers, most flavonoids possess low bioavailability by oral administration. In addition, they experience rapid metabolism in the body. After flavonoid ingestion as a form of daily food products or herbal remedy, maximum concentrations of flavonoids in the blood are expected to be generally very low (in micromolar ranges). Moreover, rapid metabolic conversion produces more hydrophilic flavonoid derivatives (flavonoid sulfates, glucuronates and/or glycosylates) that might be less active compared to their original molecules. In one study, actual plasma concentrations of orally administered flavonoids were found to be less than 1 μM except for several cases (Chen *et al*., 2005). Besides, low oral bioavailability of flavonoid ingestion has been demonstrated again and again. The maximum plasma concentration of quercetin therapeutically treated by oral administration to rats was less than 10 μM even if concentrations of various metabolites including methylated, sulfated, and glycosylated metabolites were combined (Tran *et al*., 2014). In one human study, plasma isoflavonoid (genistein) concentration in Japanese men having a high intake of genistein and genistin as soy products was approximately 0.3 μM (Adlercreutz *et al*., 1993). Several reviews have summarized findings of absorption and bioavailability of flavonoids (Ross and Kasum, 2002; Lotito and Frei, 2006). Generally, all these previous observations suggest that the low bioavailability and rapid metabolism of oral flavonoids limit their therapeutic use for acute inflammatory conditions since biologically meaningful effects of flavonoids on inflammatory response possibly will appear at concentration higher than 10 μM. Nonetheless, flavonoids may be promising therapeutics for chronic inflammatory conditions with less adverse effects as noted above
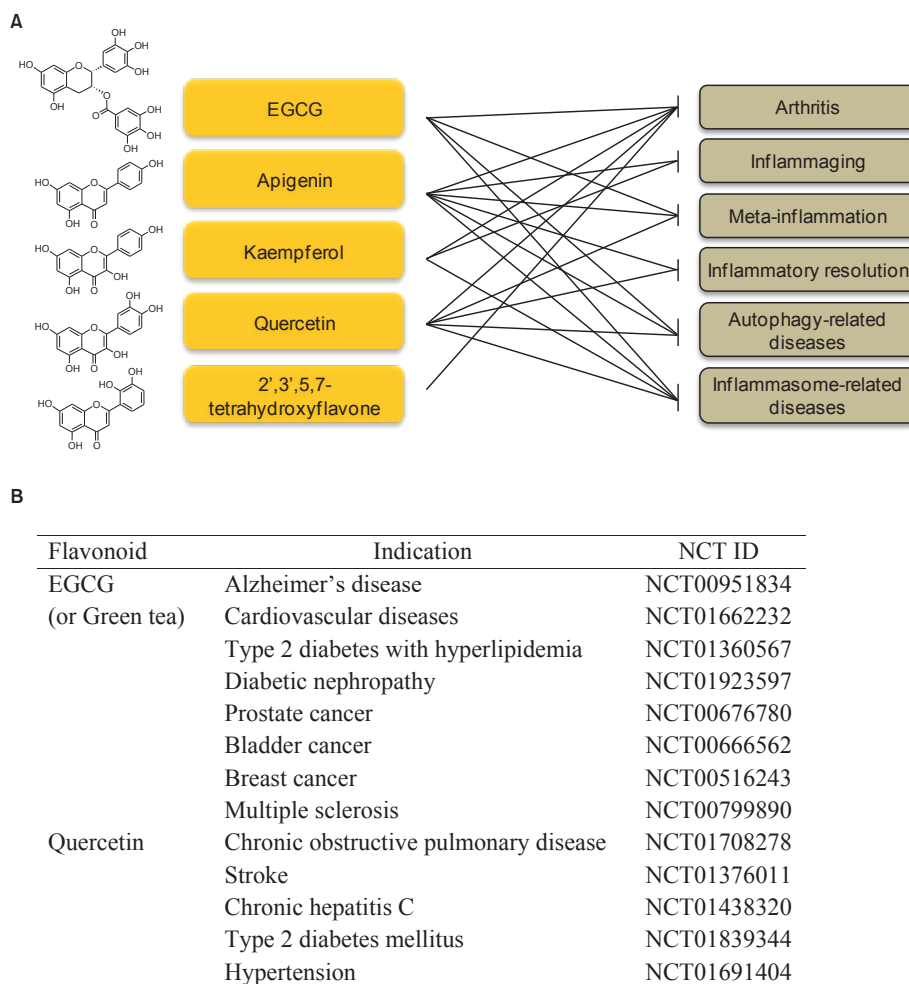
since long-term administration is needed and few appropriate therapeutic agents are available in clinics to date.

An interesting notion is that some flavonoid glucuronides among glycosylated metabolites may show significant activity in the body by conjugation and deconjugation pathway (Perez-Vizcaino *et al*., 2012). In general, glucuronide conjugates of flavonoids are known to be less active *in vivo* than those of aglycone. However, it has been proposed that glucuronidated quercetin can act as precursor of aglycone *in vivo* which could be converted to active quercetin *in situ* by β-glucuronidase (Terao *et al*., 2011; Galindo *et al*., 2012). Genistein 7-*O*-glucuronide can be converted to genistein by β-glucuronidase in inflamed mouse skin of pseudoinfection model. Such glucuronide derivative can increase phagocytic activities of macrophage (Kaneko *et al*., 2017). Glucuronidated kaempferol derivatives can inhibit several protein kinases and retain target selectivity in HepG2 cell line, although their potency is lower

than aglycone (Beekmann *et al*., 2016). These reports indicate that in therapeutic trial against inflammatory conditions, certain glucuronidated metabolites may play biologically meaningful roles by metabolic conversion *in vivo*.

FUTURE PERSPECTIVES

Flavonoids affect all phases of inflammatory processes. Although there are some limitations of flavonoids by using the oral route of administration, treatment against chronic inflammation for long-term use is possible. Moreover, high concentrations of flavonoids may be obtained more easily by local treatment. Especially, topical application through skin is one of plausible routes of flavonoid administration in human. Flavonoids may be efficiently used for skin inflammatory disorders topically if proper formulation such as nanoparticle or lipid

Flavonoid	Indication	NCT ID
EGCG	Alzheimer's disease	NCT00951834
(or Green tea)	Cardiovascular diseases	NCT01662232
	Type 2 diabetes with hyperlipidemia	NCT01360567
	Diabetic nephropathy	NCT01923597
	Prostate cancer	NCT00676780
	Bladder cancer	NCT00666562
	Breast cancer	NCT00516243
	Multiple sclerosis	NCT00799890
Quercetin	Chronic obstructive pulmonary disease	NCT01708278
	Stroke	NCT01376011
	Chronic hepatitis C	NCT01438320
	Type 2 diabetes mellitus	NCT01839344
	Hypertension	NCT01691404

Fig. 5. The suggested flavonoids with core structures showing reasonable inhibitory action on chronic inflammatory responses and clinical trials of some flavonoids. Among a variety of flavonoids, flavonoids such as EGCG, apigenin, kaempferol, quercetin, and 2',3',5,7-tetrahydroxyflavone have shown anti-inflammatory activities in many previous reports. In particular, their inhibitory actions are effective for blocking chronic inflammatory mechanisms such as arthritis, inflammaging, meta-inflammation, inflammatory resolution, autophagy and inflammasome-related diseases (A). So far, clinical trials of some flavonoids such as EGCG and quercetin have been processed for several diseases but there is a necessity of more clinical trials for chronic disorders accompanying with these inflammatory responses. Some recent completed clinical trials of flavonoids, EGCG and quercetin, are demonstrated (B). N/A, Not applicable.

nanocapsule is used (Chuang *et al*., 2017; Chamcheu *et al*., 2018; Hatahet *et al*., 2018). As noted above, applicable disorders by using flavonoid therapy are expanding. In particular, flavonoids may be used for healthy aging. Various aspects of molecular mechanisms are to be explored further. Clinical trial of certain flavonoids (Fig. 5) for these chronic inflammatory disorders is urgently needed.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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