Natural Product Sciences
10(1) : 1-10 (2004)

〈**Review**〉

Anti-inflammatory Flavonoids: Modulators of Proinflammatory Gene Expression

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Abstract – Plant flavonoids possess anti-inflammatory activity *in vitro* and *in vivo*. Although the action mechanisms are not fully understood, recent studies have clearly shown that certain flavonoids, especially flavone derivatives, express their anti-inflammatory activity at least in part by modulation of proinflammatory gene expression such as cyclooxygenase-2, inducible nitric oxide synthase and various cytokines. This review summarizes the recent findings of flavonoids modulating expression of proinflammatory molecules.
Keywords – Flavonoid, inflammation, gene expression, phospholipase, cyclooxygenase, nitric oxide synthase, interleukin.

Flavonoids (Fig. 1) are well-known plant constituents showing anti-inflammatory activity *in vitro* and *in vivo*. The cellular action mechanisms explaining their anti-inflammatory activity include antioxidative action and inhibition of arachidonic acid (AA) metabolizing enzymes such as phospholipase A_2 (PLA_2), cyclooxygenase (COX) and lipoxygenase (LOX). The inhibition of these enzymes by flavonoids leads to the reduced production of AA, prostaglandins (PG) and leukotrienes (LT), crucial mediators of inflammation. However, in recent years, many lines of evidence support the idea that certain flavonoids are the modulators of gene expression, especially the modulators of proinflammatory gene expression, thus leading to the reduced inflammatory response. Although it is not well understood how much extent in inflammation is contributed by these proinflammatory gene expressions, the suppression of these proinflammatory gene expressions is certainly one of the cellular mechanisms of anti-inflammation by flavonoids. In a previous review (Kim *et al.*, 2000), we have described *in vivo* anti-inflammatory activity and cellular action mechanisms of flavonoids. As a continual study, this paper focuses on the published data concerning the inhibition of proinflammatory enzymes and the modulation of proinflammatory gene expression by various flavonoids.

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Effects on phospholipase A_2

Arachidonic acid (AA), a precursor of eicosanoids, is generated mostly from membrane lipids in cells. The enzyme responsible for this release is phospholipase A_2, although some portion is attributed by the combined action of phospholipase C and diacylglycerol lipase. Up to date, many different forms of PLA_2 have been discovered (group I-XI) (for review, Six and Dennis, 2000). They are mainly classified into three large categories, secretory PLA_2 ($sPLA_2$), cytosolic PLA_2 ($cPLA_2$) and calcium-independent PLA_2 ($iPLA_2$). These PLA_2s are distributed in wide varieties of tissues and cells. And in some cases, they are coupled to COXs depending on the cells and agonists used (Naraba *et al.*, 1998). For instance, group IIA PLA_2 was found in arthritic synovial fluid, and group IV $cPLA_2$ are coupled to COXs and 5-LOX to produce eicosanoids. On the other hand, group VI $iPLA_2$ is thought to serve a housekeeping role in phospholipid remodeling. Therefore, a modulation of $sPLA_2$ and/or $cPLA_2$ activity is important to control the inflammatory process (Burke, 2001).

The first flavonoid inhibitor of PLA_2 found was quercetin, which inhibited group II $sPLA_2$ (Lindahl and Tagesson, 1993). And several polyhydroxylated/polymethoxylated flavonoids from Scutellaria radix were also found to inhibit group IIA PLA_2 with less inhibition against group IIB PLA_2 (Gil *et al.*, 1994). However, the most potent flavonoid inhibitors so far being found are biflavonoids. Several

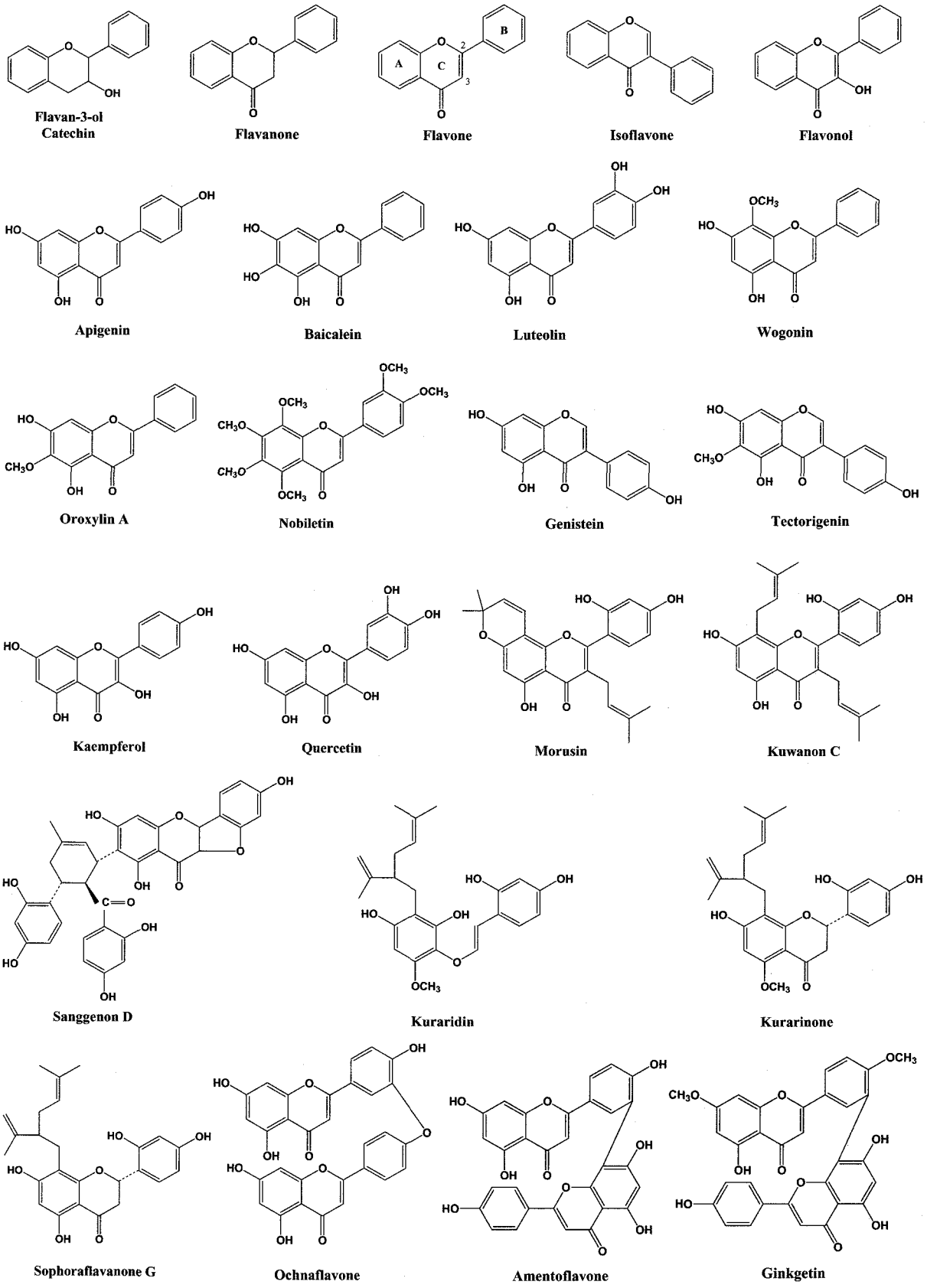


Fig. 1. Chemical structures of some representative flavonoids.

biflavones such as ochnaflavone, amentoflavone, ginkgetin and isoginkgetin were revealed to inhibit type IIA PLA_2 from rat platelets at micromolar concentrations with some selectivity over pancreatic PLA_2 (Chang *et al.*, 1994). Ochnaflavone was a noncompetitive inhibitor of group IIA PLA_2. Another biflavonoid, morelloflavone, was also proved as a $sPLA_2$ inhibitor (Gil *et al.*, 1997). It is of importance to note that biflavones such as ginkgetin and bilobetin also inhibit $cPLA_2$ (Baek *et al.*, 1999). When several flavonoids were examined, ginkgetin considerably inhibited epidermal $cPLA_2$ from guinea pig at micromolar concentrations (Kim *et al.*, 2001b). PLA_2 inhibition of biflavonoids was also proved in cells. Ginkgetin concentration-dependently inhibited AA release from the activated rat peritoneal macrophages (Lee *et al.*, 1997). These inhibitory activities of flavonoids certainly contribute to their anti-inflammatory property *in vivo*.

Effects on cyclooxygenase – COX producing PGs and thromboxanes (TX) from arachidonate, has two different isoforms at least. COX-1 is a constitutive enzyme existing in almost every cell types, affording cytoprotective PGs and blood aggregatory TXs. On the other hand, COX-2 is known as an inducible enzyme in most cases to produce large amount of PGs. COX-2 is highly expressed in inflammatory-related cell types including macrophages and mast cells, stimulated by several cytokines and/or bacterial lipopolysaccharide (LPS) (Needleman and Isakson, 1997). Therefore, COX-2 producing PGs are deeply related with inflammatory diseases of acute as well as chronic disorders. Actually, COX-2 selective inhibitors such as celecoxib possess anti-inflammatory and analgesic activity with reduced side-effects, previously encountered frequently by COX-1 or COX-1/COX-2 nonselective inhibitors (McMurray and Hardy, 2002). However, recent several investigations have shown that highly selective COX-2 inhibitors may increase cardiovascular risk, probably by TXs formed via COX-1 pathway (Crofford *et al.*, 2000). The patients are sometimes advised to take low dose aspirin in COX-2 inhibition therapy. In some respects, COX-1/COX-2 nonselective inhibitors may be more favorable compared to the use of selective COX-2 inhibitors. But, COX-2 is certainly a pivotal enzyme in inflammation and inhibitors of COX-2 are being continuously developed to obtain safer anti-inflammatory drugs.

Some flavonoids such as luteolin, morin and galangin were for the first time found as inhibitors of COX (Bauman *et al.*, 1980). After this report, intense studies have been carried out to figure out the inhibitory activity of flavonoids on COX, probably COX-1. For instance, flavonoids such as quercetin and xanthomicrol were reported to inhibit sheep platelet COX-1 (Ferrandiz *et al.*, 1990). And flavones and flavonols including chrysin, flavone, galangin, kaempferol and quercetin were revealed to inhibit TXB_2 formation from mixed leukocyte suspension (Laughton *et al.*, 1991). Recently, we have shown that amentoflavone potently inhibited COX-1 from guinea-pig epidermis with $IC_{50} = 3$ μM compared to IC_{50} of 1 μM by indomethacin (Kim *et al.*, 1998), and several prenylated flavonoids including kuraridin, kurarinone and sophoraflavanone G possess potent COX-1 inhibitory activity from bovine platelet homogenate at micromolar concentrations (Chi *et al.*, 2001b). And it was also reported that flavonoids such as genistein and kaempferol inhibited COX-1 activity (Wang *et al.*, 2000). Review papers summarizing inhibitory activity mostly against COX-1 were also available (Middleton *et al.*, 2000; Kim *et al.*, 2000). However, flavonoids inhibiting COX-2 activity have been rarely reported up to date. Several flavan-3-ols were found to weakly inhibit COX-2 at > 1 mM (pharmacologically unobtainable concentration), being more active on COX-1 (Noreen *et al.*, 1998). When various flavonoids were checked in order to find reasonably selective COX-2 inhibitors, quercetin and some prenylated flavonoids moderately inhibited COX-2, but their selectivity over COX-1 was generally low (Chi *et al.*, 2001b). Especially, morusin, kuwanon C, sanggenon B, sanggenon D and kazinol B showed moderate inhibitory activity on COX-2. These COX-2 inhibitory prenylated flavonoids, except kazinol B, have the common chemical structure, C-3 isoprenyl residue. Despite of low selectivity on COX-1, these prenylated flavonoids may have a potential for new anti-inflammatory agents since COX-1/COX-2 mixed inhibitors are preferable in some cases as mentioned above. Recently, several prenylated flavonoids including lonchoncarpol A from *Macaranga conifera* were also demonstrated to inhibit COX-1/COX-2 (Jang *et al.*, 2002). Several chalcones were revealed to be weak inhibitors of COX-1/COX-2 with no selectivity (Likhitwitayawuid *et al.*, 2002). The only selective COX-2 inhibitory flavonoid reported is wogonin, which selectively inhibits COX-2 from the homogenate of LPS-induced RAW 264.7 cells (Chi *et al.*, 2001a) without affecting COX-1 activity from human platelet homogenate (You *et al.*, 1999).

Effects on the expression of adhesion molecules – The capacity to modulate protein biosynthesis or gene expression by flavonoids was initially described that quercetin inhibited the expression of heat shock proteins (hsp72) from two different human cell lines induced by heat and some other procedures (Hosokawa *et al.*, 1990). Adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) are induced by the inflammatory stimulus and these molecules are deeply related with recruitment of inflammatory cells. Thus the regulation of expression of these molecules certainly

affects the inflammation process. Genistein (isoflavone) from soy extract was found to inhibit tumor necrosis factor-α (TNF-α)-induced up-regulation of ICAM-1 and vascular cell adhesion molecule-1 (VCAM-1) from endothelial cells (Weber *et al.*, 1995). The same compound was proved to inhibit nuclear factor-κB (NF-κB) activation in cell free system (Ishikawa *et al.*, 1995). The similar results were obtained with hydroxyflavones (especially apigenin) and flavonol (quercetin) inhibiting ICAM-1, VCAM-1 and E-selectin expression on human umbilical vein endothelial cells (HUVEC) (Gerritsen *et al.*, 1995). It is interesting to note that hinokiflavone (biflavonoid) possessed the same property, while ametoflavone did not. And various hydroxy-flavones including chrysin and apigenin were repeatedly found to inhibit VCAM-1 expression (Wolle *et al.*, 1996). Baicalein inhibited endothelial leukocyte adhesion molecule-1 (ELAM-1) and ICAM-1 expression from agonist-induced HUVEC (Kimura *et al.*, 1997 and 2001). Quercetin was repeatedly reported to suppress tetradecanoylphorbol 13-acetate (TPA)- or TNF--induced surface expression of ICAM-1 in human endothelial cells (Kobuchi *et al.*, 1999). Recently, sanggenon C was found to inhibit human polymorphonuclear leukocytes (PMN) adhesion to human synovial cells by inhibition of surface expression of ICAM-1 and VCAM-1. Activation of NF-κB was significantly inhibited by sanggenon C (Li *et al.*, 2001). All these reports clearly demonstrated that certain flavonoids possess the capacity to regulate protein expression when cells are activated with agonists or activators.

Effects on the expression of inducible nitric oxide synthase and cyclooxygenase-2 – Some flavonoids inhibited nitric oxide (NO) production from LPS-treated macrophages or macrophage cell lines such as RAW 264.7 cells. While small amount of NO synthesized by constitutive isoforms of nitric oxide synthase (NOS; eNOS, nNOS) is essential for maintaining normal body function (homeostasis), a significantly increased amount of NO synthesized by inducible isoform of NOS (iNOS) participates in provoking inflammatory process and acts synergistically with other inflammatory mediators (Nathan, 1992). Therefore, an inhibition of iNOS activity or a down-regulation of iNOS expression may be beneficial to reduce inflammatory response.

Previously, flavone and several other amino-substituted flavones were reported to inhibit NO production (Krol *et al.*, 1995). Epigallocatechin gallate was also found to weakly inhibit NO production by reducing mRNA expression of iNOS from LPS-treated RAW 264.7 cells (Chan *et al.*, 1997) and the same compound also inhibited NO production from interleukin-1β (IL-1β)-induced human chondrocytes (Singh *et al.*, 2002). Genistein was proved to inhibit LPS-induced NO production in macrophages (Sadowska-Krowicka *et al.*, 1998). Several flavonoid derivatives including apigenin, quercetin and morin also inhibited NO production from LPS-activated C6-astrocytes (Soliman and Mazzio, 1998).

In order to find action mechanisms and optimum chemical structures, structural-activity relationships were elucidated using structurally diverse flavonoid derivatives in LPS-treated RAW 264.7 cells (Kim *et al.*, 1999a). And it was found that catechins and flavanones were not active up to 100 uM. Some flavones/flavonols/isoflavones considerably inhibited NO production. On the other hand, flavonoid glycosides such as vitexin regardless of chemical structures of aglycones did not inhibit NO production up to 100 uM. In general, flavones showed strong inhibition of NO production with less inhibition by flavonols. Apigenin, wogonin and luteolin were the most active inhibitors among flavonoids tested. These results strongly suggest that C-2,3-double bond is crucial for inhibiting NO production and hydroxyl substitutions on A- and B-ring influence the inhibitory activity. A-ring 5-/7- and B-ring 3-/4-hydroxylation gave favorable results while C-3 hydroxylation (flavonol) did not. From the mechanism study, it was demonstrated that the active flavonoids did not directly inhibit iNOS enzyme activity. Instead, they significantly suppress iNOS expression, indicating that flavonoids are down-regulators of iNOS induction. In addition, the suppressive activity of quercetin, a most abundant flavonoid in nature, on NO production and iNOS induction were repeatedly described (Soliman and Mazzio, 1998; Wadsworth and Koop, 1999; Wadsworth and Koop, 2001; Raso *et al.*, 2001; Chen *et al.*, 2001, Liang *et al.*, 2001; Shen *et al.*, 2002; Cho *et al.*, 2003). In another study, broussochalcone A down-regulated iNOS induction by preventing I-κB degration to block NF-κB activation (Cheng *et al.*, 2001). Certain prenylated flavonoids such as sophoraflavanone G and some biflavones including bilobetin and ginkgetin also possess the similar property (Baek *et al.*, 1999; Cheon *et al.*, 2000; Tashiro *et al.*, 2002). And it is worth to mention that some part of the inhibitory activity of NO production by prenylated flavonoids may be associated with their cytotoxic property since most prenylated flavonoids tested showed cytotoxicity to RAW 264.7 cells at higher than 50 uM (Cheon *et al.*, 2000; Tashiro *et al.*, 2002). Recently, it was also demonstrated that silymarin (flavonolignan) down-regulated iNOS expression from LPS-treated macrophages (Kang *et al.*, 2002). All these results strongly suggest that flavonoids are natural inhibitors of iNOS induction, but not direct iNOS inhibitors.

Another importance evidence was published that apigenin, genistein and kaempferol strongly inhibited COX-2 and

iNOS induction by inhibiting NF-κB activation via I-κB kinase inhibition (Liang *et al.*, 1999; Raso *et al.*, 2001). The most active one among the tested compounds was apigenin. However the derivatives including apigenin did not directly inhibit COX-2 enzyme activity. Isoflavones, tectorigenin and tectoridin from Belamcamda radix, were also proved to inhibit COX-2 expression and PGE_2 production from peritoneal macrophages (Kim *et al.*, 1999b). Oroxylin A (flavone) from Scutellaria radix possessed the same property of COX-2 and iNOS suppression through inhibition of NF-κB activation (Chen *et al.*, 2000). In other experiment using gene-reporter assay to express COX-2, quercetin, rhamnetin, genistein and luteolin were proved to be active inhibitors, but ECGC, catechin and myricetin were not (Mutoh *et al.*, 2000). Nobiletin also reduced production of PGE_2 by down-regulating COX-2 (Murakami *et al.*, 2000; Lin *et al.*, 2003). Biflavonoids including bilobetin and ginkgetin down-regulate COX-2 induction from LPS-induced RAW 264.7 cells (Baek *et al.*, 1999). Another biflavonoid, amentoflavone, also down-regulates COX-2 in TNF-α-induced A549 cells (Banerjee *et al.*, 2002). These previous studies have demonstrated that many flavone derivatives inhibit COX-2 suppression, resulting in reduced prostanoid production and reduced inflammatory response.

The structural-activity relationship of flavonoids for COX-2 down-regulation is not clear. As in the case of iNOS down-regulation, certain flavonoid derivatives such as apigenin and luteolin showed higher inhibitory activity of COX-2 expression compared to the flavonol derivatives including quercetin. A C-2,3-double bond and patterns of hydroxylation/methoxylation on A- and B-ring seem to be important. The particular interest is wogonin (5,7-dihydroxy-8-methoxyflavone) isolated from Scutellaria radix. As noted above, wogonin was proved to be a most potent inhibitor of NO production. Wogonin was repeatedly found to inhibit NO production by iNOS from LPS-induced macrophages (Kim *et al.*, 1999a; Wakabayashi, 1999; Kim *et al.*, 2001a; Chen *et al.*, 2001; Chi *et al.*, 2001a; Shen *et al.*, 2002). Especially, this compound was revealed as a down-regulator of iNOS and COX-2. Furthermore, it has a direct inhibitoy activity of COX-2 without affecting COX-1 activity (You *et al.*, 1999; Wakabayashi and Yasui, 2000; Chi *et al.*, 2001a). Although the general property of down-regulation by wogonin was similar with those of steroidal anti-inflammatory drug, the same flavonoid was revealed not to use glucocorticoid receptor for expressing its activity (Chi *et al.*, 2001a). Wogonin, on the other hand, was reported to increase TNF-α and iNOS m-RNA in normal RAW cells at low concentrations (≅1 μM) (Chiu *et al.*, 2002). These results indicate that wogonin (maybe some other flavonoids) acts differentially depending on the cell status, normal or activated.

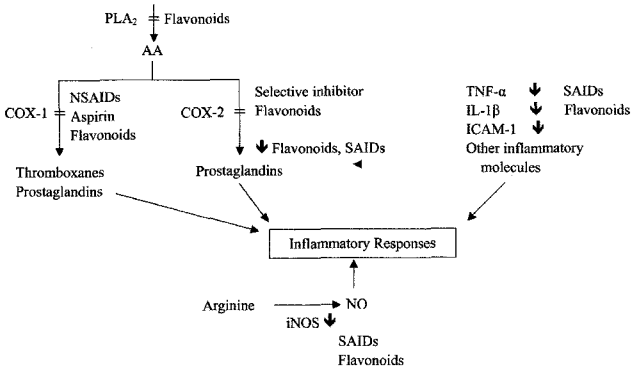
Effects on the expression of other proinflammatory molecules – In addition to COX-2/iNOS, several cytokines are deeply associated with inflammatory diseases. In particular, TNF-α and IL-1β are prominent contributors to chronic inflammatory disorder including rheumatoid arthritis. Genistein was reported to down-regulate IL-1β, IL-6 and TNF-α in LPS-induced human blood monocytes (Geng *et al.*, 1993). Amoradicin, genistein and silybin were proved to inhibit TNF-α production from LPS-treated RAW 264.7 cells (Cho *et al.*, 2000). It was observed that wogonin prevented IL-1β and TNF-α induction from LPS-treated RAW 264.7 cells (unpublished results). A recent study also revealed that wogonin inhibited IL-6 and IL-8 production from IL-1β-treated human retinal pigment epithelial cell line (Nakamura *et al.*, 2003). By super antigen treatment, baicalin was found to inhibit IL-1β, IL-6, TNF-α, IFN-γ, monocyte chemotactic protein-1, macrophage inflammatory protein (MIP)-1 and MIP-1 induction at protein as well as at RNA levels in human peripheral blood mononuclear cell culture (Krakauer *et al.*, 2001). In human fibroblasts induced by IL-4 plus TNF-γ, baicalein>oroxylin A>baicalin >skullcapflavone II inhibited eotaxin production (Nakajima *et al.*, 2001). Some flavonoids such as fisetin were recently revealed to inhibit T_H2-type cytokine production including IL-4, IL-13 and IL-5 by activated human basophils (Higa *et al.*, 2003). All these results strongly suggest the favorable effect of flavonoids on improving clinical symptoms of inflammatory and allergic diseases.

Cellular action mechanisms – The cellular action mechanisms of flavonoids for modulating gene expression have been actively studied. The most prominent points of cellular regulation by flavonoids are various kinases including protein kinase C (PKC) and mitogen activated protein kinase (MAPK). Through the inhibition of these enzymes, DNA-binding capacity of transcription factors such as NF-κB or AP-1 is regulated. Thereby, the expression of target genes is regulated. Flavonoids were reported to inhibit the enzyme activity of various signal transduction kinases. The best example is PKC inhibition (Ferriola *et al.*, 1989) and protein tyrosine kinase inhibition (Chang and Geahlen, 1992) by various flavonoid derivatives. Quercetin has been revealed to inhibit IκB-kinase (Liang *et al.*, 1999). It was also reported that quercetin inhibited TNF-α-induction from LPS-induced RAW cells by inhibiting Jun N-terminal kinase (JNK)/stress activated protein kinase (SAPK), leading to the inhibition AP-1-DNA binding (Wadsworth *et al.*, 2001). In a separate pathway, quercetin inhibited extracellular signal related kinase (ERK) 1/2 and p38 MAPK to regulate

post-transcriptional level of TNF-α. Recently, it has been also shown that quercetin inhibited NF-κB activation by ERK and p38 kinase inhibition (Cho *et al.* 2003). Wogonin inhibited monocyte chemotactic protein-1 gene expression of TPA-induced human endothelial cells by AP-1 repression through ERK 1/2 and JNK inhibition (Chang *et al.*, 2001). In another study, wogonin inhibited NF-κB activation from C6-glial cells (Kim *et al.*, 2001a) and from human retinal pigment epithelial cells (Nakamura *et al.*, 2003). Some other flavonoids including genistein (Geng *et al.*, 1993; Baxa and Yoshimura, 2003), apigenin, kaempferol (Liang *et al.*, 1999), oroxylin A (Chen *et al.*, 2000), broussochalcone A (Cheng *et al.*, 2001), silymarin (Kang *et al.*, 2002), epigallocatechin 3-gallate (Singh *et al.*, 2002) and amentoflavone (Banergee *et al.*, 2002) inhibited NF-κB activation. In Rat-1 fibroblasts, luteolin inhibited LPS-stimulated interaction between the p65 subunit of NF-κB and the transcriptional coactivator, CREB-binding protein (Kim *et al.*, 2003) and in RAW 264.7 cells, the same compound inhibited several MAP kinases such as ERK, p38 and CK2 (Xagorari *et al.*, 2002).

All of the above results have clearly shown that flavonoids may inhibit the expression of various inflammation-related proteins/enzymes, at least partly, by suppressing activation of transcriptional factors such as NF-κB and AP-1. This suppression might be mediated via inhibition of several protein kinases involved in signal transductin pathway. Some evidences were also demonstrated that flavonoids modulate peroxisome proliferator-activated receptor-γ (Liang *et al.*, 2001) and acts as inhibitors of proteosome activity (Kazi *et al.*, 2003). The detailed and common mechanisms of flavonoids need to be elucidated further in near future.

***In vivo* effects on the expression of proinflammatory molecules** – Although above numerous studies clearly demonstrated that certain flavonoids are regulators of proinflammatory gene expression *in vitro*, there have been only a few investigations to prove the same effects of flavonoids *in vivo*. For example, apigenin inhibited ICAM-1 expression in TNF-α-treated mice (Panes *et al.*, 1996). Flavonoids such as quercetin and rutin were found to suppress lethal endotoxic shock induced by LPS or LPS plus D-galactosamine in mice (Takahashi *et al.*, 2001). They reduced TNF-α production. Another example is silymarin, which inhibited ornithine decarboxylase mRNA on SKH-1 hairless mouse skin (Katiyar *et al.*, 1997). The same compound was also reported to inhibit COX-2 and IL-1α induction on SENCAR mouse epidermis treated with TPA (Zhao *et al.*, 1999). In LPS-treated mice, luteolin intraperitoneally administered increased survival and inhibited the expression of TNF-α and ICAM-1 (Kotanidou *et al.*, 2002). When administered intraperitoneally in mice, wogonin inhibited lethal shock induced by LPS and D-galactosamine. It inhibited TNF-α production (Dien *et al.*, 2001). By our group, wogonin topically applied was for the first time proved to inhibit COX-2 induction on mouse skin induced by TPA (Park *et al.*, 2001). Recently, wogonin intravenously injected was proved to inhibit *in vivo* production of NO by LPS treatment (Shen *et al.*, 2002). But, the same compound did not reduce PGE_2 production and induction of COX-2. This study suggests some interesting property of wogonin. Wogonin clearly inhibited COX-2 induction by topical treatment on the skin, while wogonin in the systemic circulation may be converted rapidly to metabolites, which could affect iNOS induction, but not COX-2. Moreover, wogonin topically applied did strongly inhibit COX-2 and TNF-α induction with less inhibition of ICAM-1 and IL-1β expression on mouse skin treated by TPA (Chi *et al.*, 2003). The similar inhibition of COX-2 induction on TPA-treated mouse skin was observed by biflavonoids, ginkgetin and isoginkgetin, when topically applied (Kwak *et al.*, 2002).



Scheme 1. A proposed action mechanism of flavonoids NSAID (nonsteroidal anti-inflammatory drug), SAID (steroidal anti-inflammatory drug), "=" and " ↓ " denote enzyme inhibition and down-regulation of the expression, respectively.

In conclusion, all these previous findings have demonstrated that the modulation of proinflammatory gene expression is certainly one of major action mechanism(s) of flavonoids showing anti-inflammatory activity (Scheme 1). Unlike nonsteroidal anti-inflammatory drugs (NSAID) such as indomethacin, these modulating activities are unique and new to anti-inflammatory flavonoids. Moreover, being nature's tender drugs, flavonoids may show no or minimum adverse effect on human use. Therefore, plant flavonoids are reasonable candidates for the development of new anti-inflammatory drugs. To achieve this goal, it is necessary to find flavonoid molecules having optimal chemical structures and significant anti-inflammatory activity enough for a clinical trial through continuing research.

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(Accepted January 30, 2003)