





## Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease

Ana García-Lafuente  Eva Guillaumon   
Ana Villares  Mauricio A. Rostagno   
José Alfredo Martínez

Received: 1 October 2008 / Revised: 9 January 2009 / Accepted: 16 March 2009 / Published online: 21 April 2009  
© Birkhäuser Verlag, Basel/Switzerland 2009


**Abstract** Chronic inflammation is being shown to be increasingly involved in the onset and development of several pathological disturbances such as arteriosclerosis, obesity, diabetes, neurodegenerative diseases and even cancer. Treatment for chronic inflammatory disorders has not been solved, and there is an urgent need to find new and safe anti-inflammatory compounds. Flavonoids belong to a group of natural substances occurring normally in the diet that exhibit a variety of beneficial effects on health. The anti-inflammatory properties of flavonoids have been studied recently, in order to establish and characterize their potential utility as therapeutic agents in the treatment of inflammatory diseases. Several mechanisms of action have been proposed to explain *in vivo* flavonoid anti-inflammatory actions, such as antioxidant activity, inhibition of eicosanoid generating enzymes or the modulation of the production of proinflammatory molecules. Recent studies have also shown that flavonoids are modulators of proinflammatory gene expression, thus leading to the attenuation of the inflammatory response. However, much work remains to be done in order to achieve definitive conclusions about their potential usefulness. This review summarizes the known mechanisms involved in the anti-inflammatory activity of flavonoids and the implications of these effects on the protection against cancer and cardiovascular disease.

**Keywords** Flavonoids · Inflammation · Cancer · Cardiovascular disease

---

Responsible Editor: J. S. Skotnicki.

---

A. García-Lafuente  · E. Guillaumon · A. Villares · M. A. Rostagno · J. A. Martínez  
Centro para la Calidad de los Alimentos,  
Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria (INIA), Campus Universitario "Duques de Soria",  
42071 Soria, Spain  
e-mail: garcia.ana-maria@inia.es

Although steroidal anti-inflammatory drugs and NSAIDs are currently used to treat acute inflammation, these drugs have not been entirely successful in curing chronic inflammatory disorders while such compounds are accompanied by unexpected side effects. Therefore, there is an urgent need to find safer anti-inflammatory compounds<sup>4</sup>. Traditional medicine has used extracts of different plants for the treatment of a wide variety of disorders including acute and chronic inflammation. Among the active constituents of these extracts, flavonoids are a family of substances whose members have many interesting biological properties

including anticancer, antimicrobial, antiviral, anti-inflammatory, immunomodulatory, and antithrombotic activities [5–7]. Many investigations have repeatedly proven that flavonoid molecules exhibit anti-inflammatory functions. Thus, the anti-inflammatory activities of avonols (quercetin, rutin and morin) and avanones (hesperetin and hesperidin) were investigated in acute and chronic inflammation animal models [8]. Rutin was only effective in the chronic process, principally in adjuvant arthritis. On exhibit anti-inflammatory activity both, in vitro and in various animal models of inflammation [8, 9].

Among these biological activities, the anti-inflammatory capacity of flavonoids has long been utilized in Chinese and Western medicine by applying crude plant extracts. Many investigations have shown that a variety of flavonoid molecules exhibit anti-inflammatory activity both, in vitro and in various animal models of inflammation [8, 9].

In addition, inflammation is increasingly found to be involved in the development of several chronic diseases such as arteriosclerosis, obesity, diabetes, neurodegenerative diseases and even cancer. Among them, cardiovascular diseases and cancer are main causes of mortality in many countries. Numerous epidemiological studies indicate that an increase in the consumption of flavonoid-rich fruits and vegetables is associated with a decrease in the incidence of cardiovascular disease and different types of cancer [10]. This protective effect has been attributed in part to the anti-inflammatory properties of flavonoids [16]. Thus, it may be valuable to study the anti-inflammatory activity of flavonoids, not only in order to establish anti-inflammatory mechanisms, but also for developing a new class of anti-inflammatory agents, which may be useful in the treatment of these kind of diseases [7].

This document reviews the anti-inflammatory properties of flavonoids with special emphasis on the various mechanisms potentially implicated. We also summarize the central role that inflammation plays in the onset and progression of two of the most important diseases of the world: cancer and cardiovascular disease. The possible effects of flavonoids in the prevention and treatment of such diseases are also reviewed, on the basis of their anti-inflammatory activity.

## Flavonoids and inflammation

Flavonoids are a polyphenols subclass which are widely distributed in the plant kingdom, and are characterized by two or more aromatic rings, each bearing at least one aromatic hydroxyl and connected with a heterocyclic pyran [18]. Flavonoids are categorized into different subtypes based on the connection of an aromatic ring to the heterocyclic ring as well as the oxidation state and functional groups of the heterocyclic ring. Flavonoids are found in fruits, vegetables, legumes, herbs, spices, stems, flowers as well as tea and red wine. They are prominent components of citrus fruits and other food sources and are in many countries regularly consumed in a healthy diet. Table 1 shows the subclasses of flavonoids and names of prominent food flavonoids and typical food sources [8].

Flavonoids are a polyphenols subclass which are widely distributed in the plant kingdom, and are characterized by two or more aromatic rings, each bearing at least one aromatic hydroxyl and connected with a heterocyclic pyran [18]. Flavonoids are categorized into different subtypes based on the connection of an aromatic ring to the heterocyclic ring as well as the oxidation state and functional groups of the heterocyclic ring. Flavonoids are found in fruits, vegetables, legumes, herbs, spices, stems, flowers as well as tea and red wine. They are prominent components of citrus fruits and other food sources and are in many countries regularly consumed in a healthy diet. Table 1 shows the subclasses of flavonoids and names of prominent food flavonoids and typical food sources [8].

Several mechanisms explaining the anti-inflammatory activity of flavonoids have been described, including (a) antioxidant and radical scavenging activities, (b) regulation of cellular activities of inflammation-related metabolism enzymes (phospholipase A2, cyclooxygenase,

Table 1 Subclasses and prominent food avonoids and typical food sources

Flavonoid subclass	Food avonoid	Food source
Flavanols	Catechin, galliccatechin, epicatechin	Teas, red grapes and red wines
Flavanones	Naringenin, hesperetin, eriodictyol	Citrus foods
Flavones	Apigenin, luteolin	Green leafy spices
Iso avones	Daidzein, genistein, glycitein, biochanin A	Soybeans, soy foods, and legumes
Flavonols	Kaempferol, myricetin, quercetin, isorhamnetin	Nearly ubiquitous in foods
Anthocyanidins	Cyanidin, delphinidin, pelargonidin	Red, purple and blue berries

lipoyxygenase) and nitric oxide synthase, (d) modulation of hydroxyl radical, peroxy radicals, hypochlorous acid and the production of other proinflammatory molecules, (e) peroxynitrous acid, since they are oxidized by radicals, modulation of proinflammatory gene expression.

Flavonoids as antioxidants

Body cells and tissues are continuously threatened by the peroxynitrite [35]. Epicatechin and rutin have a powerful damage caused by free radicals and reactive oxygen species, hydroxyl radical (OH) scavenging effect, about 100–300 which are produced during normal oxygen metabolism or are times higher than mannitol, a typical ROS scavenger, and induced by exogenous factors [24]. The increased production also inhibit the superoxide anion (O<sub>2</sub><sup>-</sup>) generation in the of reactive oxygen species accompany most forms of tissue injury, which have been implicated in a multitude of disease states ranging from inflammatory injury to myocardial infarction and cancer [25]. The mechanisms and the preventive actions against atherosclerosis sequence of events by which free radicals interfere with cellular functions are not fully understood, but some of the detrimental effects in biological systems include peroxidation of membrane lipids, oxidative damage to nucleic acids or carbohydrates and the oxidation of sulfhydryl and other susceptible groups in proteins [26, 27]. In addition, free radicals can attract various inflammatory mediators contributing to a generalized inflammatory response and tissue damage. Indeed, flavonoids are powerful in vitro antioxidants, being able to scavenge a wide range of free radical species, as well as to inhibit their formation.

Effect on ROS production by phagocytic cells

Phagocytosis is an important physiological process accompanied by the production of superoxide anion to peroxynitrite-mediated oxidation, in vitro, in a concentration-dependent fashion [35]. While ROS generated by phagocytes play an important physiological function, they can also cause cellular damage. The highly reactive oxygen species, along with other mediators elaborated by neutrophils and macrophages, promote inflammation and cause tissue damage [28, 29]. Several flavonoids have been shown to be effective inhibitors of ROS production by activating human neutrophils [30–32].

Radical scavenging

Flavonoids are scavengers of a wide variety of reactive oxygen, nitrogen, and chlorine species such as superoxide

resulting in a more stable, less reactive radical [33]. Selected flavonoids can directly scavenge superoxide [34], whereas other flavonoids such as genistein and daidzein can scavenge the highly reactive oxygen-derived radical peroxyl radical (OH) scavenging effect, about 100–300 times higher than mannitol, a typical ROS scavenger, and also inhibit the superoxide anion (O<sub>2</sub><sup>-</sup>) generation in the xanthine-xanthine oxidase system [36]. By scavenging radicals, flavonoids can inhibit LDL oxidation in vitro [37] protecting the LDL particles. Such effect may have preventive actions against atherosclerosis. During inflammation, high concentrations of nitric oxide produced by inducible nitric oxide synthase in macrophages can result in oxidative damage. In such circumstances, activated macrophages greatly increase the simultaneous production of both nitric oxide and superoxide anions. Nitric oxide reacts with free radicals, thereby directly oxidize LDL, resulting in irreversible damage to the cell membrane [34]. When flavonoids are used as antioxidants, free radicals are scavenged and, therefore, can no longer react with nitric oxide, resulting in less cellular damage [38]. Also, nitric oxide can be viewed as a radical itself, and it has been reported that nitric oxide molecules are directly scavenged by flavonoids [39]. The soybean isoflavones genistein and daidzein increase LDL resistance to peroxynitrite-mediated oxidation, in vitro, in a concentration-dependent fashion [35]. In vivo experiments have demonstrated that oral administration of isoflavones and extracts from soy-based products decrease serum nitrite, nitrate and nitrotyrosine levels in LPS-induced rats [40]. Thus, isoflavone supplementation may inhibit reactive nitrogen species-induced oxidation, helping to provide a protective effect against cardiovascular and chronic inflammatory diseases.

Inhibition of pro-oxidant enzymes

Stimulation of inflammatory cells such as macrophages by bacterial endotoxins or inflammatory cytokines results in

increased expression of inducible nitric oxide synthase (iNOS) and subsequent production of large amount of nitric oxide that is able to produce oxidative injury. Flavonoids such as genistein correlated with a reduced IL-2 secretion and IL-2R expression in T cells stimulated with PHA/PMA. Also, PTK activation is required for LPS induction and activity in cultured macrophages by reducing the release of cytokines such as TNF- $\alpha$ , IL-6 and IL-1 $\beta$  from human blood monocytes. In in vitro studies with human peripheral mononuclear cells, genistein at a non-cytotoxic concentration, inhibited cell proliferation, and oxidizing molecules other than their regular substrates such as L-2 and LTB4 production from stimulated cultures with the potential for increasing oxidative lesion in some tissues. Some flavonoids and other plant polyphenols have been shown to increase in mRNA of IL- $\beta$ , IL-6 and TNF- $\alpha$  produced by the ability to inhibit cyclooxygenase (COX-2) and LPS-stimulated monocytes was blocked by genistein, lipoxigenase [43–45].

The xanthine oxidase pathway has been implicated as a major source of reactive oxygen species (ROS) in the important route in the oxidative injury to tissues. During ischemic conditions, xanthine dehydrogenase changes to xanthine oxidase that is a source of oxygen free radicals. Some flavonoids inhibit xanthine oxidase activity, resulting in decreased oxidative injury. Other flavonoids such as apigenin, chrysin or luteolin and flavonols such as kaempferol and quercetin showed remarkable antiproliferative effects on M-CSF-activated macrophages, which may be related with their role as tyrosine kinase inhibitors are implicated in the pathogenesis of chronic inflammatory diseases, since polyphenolic components from dietary plants may increase the endogenous antioxidant potential and, thus, modulate cellular redox state. These compounds may be an alternative for the treatment of chronic inflammatory diseases.

Indeed, a variety of oxidants, free radicals and aldehydes are implicated in the pathogenesis of chronic inflammatory diseases, since polyphenolic components from dietary plants may increase the endogenous antioxidant potential and, thus, modulate cellular redox state. These compounds may be an alternative for the treatment of chronic inflammatory diseases.

#### Modulation of inflammatory related cell functions

The immune system is integrated by a highly complex group of cells that may interact in a cell-cell manner and may also respond to intercellular messages including hormones, cytokines and autacoids. The immune response can be modified by diet, pharmacological agents, environmental pollutants, and naturally occurring food chemicals such as vitamins and flavonoids. Some flavonoids display a remarkable array of biochemical and pharmacological actions that affect the function of immune cells and in inflammatory cells such as T cells, B cells, macrophages, neutrophils, mast cells, or basophils.

Several flavonoids specifically affect enzyme systems critically involved in the generation of inflammatory processes, especially tyrosine and serine-threonine protein kinases. These enzymes are involved in signaling transduction and cell activation processes such as T cell proliferation [51, 52], B lymphocyte activation [53] or cytokine production by stimulated monocytes [54].

Genistein, an isoflavone, has been demonstrated as a specific inhibitor for tyrosine protein kinase [55]. This activity may be involved in some of its anti-inflammatory effects, while T cell proliferation is accompanied by phosphorylation of tyrosine of particular T cell proteins. Trevillyan

et al. [56] showed that the inhibition of the enzymatic activity of the T cell specific protein kinase p56lck by genistein correlated with a reduced IL-2 secretion and IL-2R expression in T cells stimulated with PHA/PMA. Also, PTK activation is required for LPS induction and activity in cultured macrophages by reducing the release of cytokines such as TNF- $\alpha$ , IL-6 and IL-1 $\beta$  from human blood monocytes [54, 57]. In in vitro studies with human peripheral mononuclear cells, genistein at a non-cytotoxic concentration, inhibited cell proliferation, and oxidizing molecules other than their regular substrates such as L-2 and LTB4 production from stimulated cultures with the potential for increasing oxidative lesion in some tissues. Some flavonoids and other plant polyphenols have been shown to increase in mRNA of IL- $\beta$ , IL-6 and TNF- $\alpha$  produced by the ability to inhibit cyclooxygenase (COX-2) and LPS-stimulated monocytes was blocked by genistein, lipoxigenase [43–45].

factor  $\kappa$ B (NF- $\kappa$ B), a transcription factor involved in the expression of cytokine genes, illustrating a potentially very important flavonoid–gene interaction. Other flavonoids such as apigenin, chrysin or luteolin and flavonols such as kaempferol and quercetin showed remarkable antiproliferative effects on M-CSF-activated macrophages, which may be related with their role as tyrosine kinase inhibitors are implicated in the pathogenesis of chronic inflammatory diseases, since polyphenolic components from dietary plants may increase the endogenous antioxidant potential and, thus, modulate cellular redox state. These compounds may be an alternative for the treatment of chronic inflammatory diseases.

Oral administration of rutin reduced neutrophils chemotaxis to FMLP in a model of rat paw oedema [63]. Several flavonoids such as luteolin, kaempferol, apigenin, or quercetin have been reported as potent inhibitors of  $\beta$ -glucuronidase and lysozyme release from neutrophils [64]. These flavonoids significantly inhibited arachidonic acid release from membranes, an effect that was correlated with degranulation [64].

Many investigations have shown that different flavonoid molecules modulate the activity of arachidonic acid (AA) metabolizing enzymes such as phospholipase (PLA<sub>2</sub>) and cyclooxygenase (COX) and lipoxigenase (LOX) [65, 66], and the nitric oxide (NO) producing enzyme, nitric oxide synthase (NOS) [68, 69]. The inhibition of these enzymes reduces the production of AA, prostaglandins, leucotrienes, and NO, which are crucial mediators of inflammation. Thus, the inhibition of these enzymes by flavonoids may be one of the most important mechanisms of their anti-inflammatory activity.

#### Modulation of proinflammatory enzyme activities

*Arachidonic acid related enzymes*

Arachidonic acid release is a starting point for a general inflammatory response. Arachidonic acid is released from membrane phospholipids in cells by the action of phospholipase A<sub>2</sub> (PLA<sub>2</sub>) and metabolized by cyclooxygenase (COX) and lipoxygenase (LOX) pathways to prostaglandins, vasoactive leukotrienes LTC<sub>4</sub>, LTD<sub>4</sub>, LTE<sub>4</sub>, as well as to the potent chemoattractant LTB<sub>4</sub> [50]. Selected phenolic compounds such as flavonols and polyphenols were found to inhibit these enzymes, reducing the release and metabolism of arachidonic acid and thus, diminishing the formation of inflammatory mediators.

The first described flavonoid inhibitor of PLA<sub>2</sub> was quercetin, which inhibited PLA<sub>2</sub> from human neutrophils [70]. Later, several studies have repeatedly reported that quercetin and other flavonoids inhibit different isoforms of PLA<sub>2</sub> from different sources [65, 66, 71, 72].

Cyclooxygenase (COX) produces prostaglandins (PGs) and thromboxanes from AA. The enzyme exists in two different isoforms COX-1 and COX-2. Thus, COX-1 is a constitutive enzyme existing in almost every cell type, while COX-2 is an inducible enzyme that produces large quantities of PG, and is highly expressed in the inflammation related cells when they are stimulated with proinflammatory cytokines and/or bacterial lipopolysaccharide [73, 74].

Lipoxygenases (LOXs) are responsible for generating hydroxy acids and leukotrienes from AA. Among the different isoforms of LOX, 5- and 12-LOX are involved in allergic and inflammatory disorders, 5-LOX produces 5-HETE and LTs, which are potent chemoattractants, 12-LOX synthesizes 12-HETE, which aggregate platelets and induces inflammatory responses [75].

Some flavonoids such as luteolin, galangin or morin were for the first time described as inhibitors of COX [76]. From human thrombin aggregated platelets, certain flavonoids were identified as COX/LOX inhibitors, and this antagonistic activity was related with the structural characteristics of the different molecules: flavone derivatives such as flavone, apigenin, and chrysin inhibited platelet aggregation by depressing the COX pathway, while flavonol-related compounds such as myricetin and quercetin inhibited primarily LOX activity [77].

Flavonoids inhibiting COX-2 activity has been rarely reported, Chi et al. [67] compared the effect of different flavonoid derivatives on COX-1, COX-2, 5-LOX and 12-LOX activity. Among the studied molecules some prenylated flavonoids moderately inhibited COX-2, but with low selectivity over COX-1. Wogonin, a plant derived flavone was found to inhibit COX-2 activity as well as COX-2 expression in LPS induced macrophages [78, 79]. This compound did not significantly inhibit COX-1 and 12-LOX from human platelet homogenates [80]. The inhibitory effect of wogonin on COX-2 activity may be a selective effect, since this compound inhibits PGE<sub>2</sub> production, but not LTB<sub>4</sub> from IL-1 $\beta$  induced gingival fibroblasts [81]. The inhibition of 5-LOX from human polymorphonuclear cells by flavonoids has been investigated [82]. Thus, it has been shown that flavonoids act as redox inhibitors that can regulate lipoxygenase activity by preventing activation of resting form (ferrous state) to its reactive state (ferric) and simultaneously can convert the active form of lipoxygenase to its resting state. Among the molecules studied, genistein was a more potent inhibitor of LOX than daidzein, while glycosylated forms were as potent as their aglycones [82].

The LOX pathway generates leukotrienes. When COX-2 is blocked, the LOX pathway still produces the potent mediators of inflammation. Dual inhibition of COX/LOX has been suggested to be a relevant approach in the development of new anti-inflammatory treatments [83].

Some natural polyphenols such as curcumin are inhibitors of both COX and LOX. These compounds can modulate arachidonic acid metabolism at different stages, by inhibiting phosphorylation of cPLA<sub>2</sub>, inhibiting COX-2 protein expression and catalytic activity, and inhibiting 5-LOX activity [83].

*NO synthase*  
NO, a ubiquitous cellular mediator of physiological and pathological processes, is produced by a family of enzymes, including endothelial NOS (eNOS), neuronal NOS (nNOS) and inducible NOS (iNOS). The latter type is an inducible enzyme that is highly activated by inflammatory stimuli (LPS and inflammatory cytokines) in certain cells such as macrophages [84].

Indeed, iNOS is responsible for the overproduction of NO during inflammation. Thus, compounds that are able to reduce NO production by iNOS without affecting eNOS or nNOS may be desirable as anti-inflammatory agents. Certain flavonoids have been shown to inhibit NO production from macrophage or macrophage-like cells activated with inflammatory stimuli [85-89]. In this context, it has been reported that the high affinity of polyphenols for proteins and a possible subsequent conformational change of enzyme might be associated with the inhibitory effect by flavonoids on iNOS enzyme activity [68]. However, only a few studies have demonstrated a direct effect of flavonoids on enzyme activity. Cheon et al. (2000) studied the effects of some prenylated flavonoids and biflavonoids on LPS-induced nitric oxide production from RAW 264.7 cell line. These investigators found that such compounds inhibited the production of nitric oxide, this effect being mediated by the suppression of iNOS enzyme induction, but not by direct inhibition of

iNOS activity. The only reported exception was echinoid contribute to the inflammatory response but is evident that so avone, which inhibited iNOS enzyme activity and avonoids show anti-inflammatory activity, at least in part, suppressed iNOS enzyme induction [69]. Studies with soy by affecting mRNA levels. The mechanisms by which iso avones genistein, daidzein and glycitein have revealed avonoids block proinflammatory gene expression are that all of them are able to dose-dependently suppress NO. Currently being investigated, but pioneer studies suggest an production in LPS-activated murine macrophages by three effect on transcriptional activity suppression in response to different mechanisms: scavenging of NO radicals, inhibition of inflammatory stimuli [97].

tion of iNOS enzyme activity and inhibition of iNOS gene COX-2 selective inhibitors are claimed to show anti-inflammatory activity and are continuously being developed to obtain safer anti-inflammatory drugs. Flavonoids to a direct effect on enzyme activity, but was through inhibiting COX-2 activity are rarely reported, but some reduction of iNOS enzyme expression [67, 90].

#### Modulation of the production of other proinflammatory molecules

In addition to COX-2 and iNOX, several cytokines are avones and avonols were active suppressors, but epideeply associated with inflammatory diseases. In particular gallic acid, catechin, and myricetin were not lar, tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), IL-6 and IL-1 $\beta$  are [98]. In a recent work, Hooshmand et al [99] have found prominent contributors to chronic inflammatory responses. that genistein selectively decreases the production of LPS-Genistein was reported to inhibit IL-1 $\beta$ , IL-6 and TNF- $\alpha$  induced COX-2 protein level in chondrocytes without production in LPS-induced human blood monocytes affecting COX-1. Luteolin decreases protein and mRNA [54]. The inhibitory effect of genistein on IL-6 production levels of the proinflammatory iNOS and COX-2 in LPS-

has been shown in different settings: cultured human stimulated macrophages [100]. intestinal cells Caco-2 [9], osteoblast cells [91], human gastric epithelial cells [92], or macrophages [93]. Pre-treatment of the macrophage cell line RAW 264.7 with [89]. Hämmäinen et al. compared the effects of a series of luteolin, luteolin-7-glucoside, quercetin, and genistein compounds on NO production. The avonoid classes inhibited both LPS-stimulated TNF- $\alpha$  and IL-6 release, containing the most effective compounds were iso avones and avonols. They identified eight compounds as being able to inhibit LPS-induced iNOS expression: avones, daidzein, genistein, isorhamnetin, kaempferol, quercetin, naringenin and pelargonidin [101].

The comparison of molecular structures from different avonoids shows that the presence of a double bond at position C2–C3 of the C ring with oxo function at position 4, along with the presence of OH groups at position 4' of the B ring, are required for optimal inhibition of LPS-stimulated TNF- $\alpha$  release [93].

Amoradin, genistein, and silybin were shown to inhibit TNF- $\alpha$  production from LPS-treated RAW 264.7 cells [94]. Quercetin inhibited IL-1 $\beta$ , IL-6 and TNF- $\alpha$  production in LPS-stimulated RAW 264.7 cells [95]. Wogonin reduces the in vitro TNF- $\alpha$  production in LPS stimulated RAW cells and decreases the in vivo level of circulating TNF- $\alpha$  in mice administered  $\alpha$ -galactosamine and LPS [96].

#### Modulation of proinflammatory gene expression

In recent years, several lines of evidence have supported the idea that certain avonoids are modulators of proinflammatory gene expression, thus leading to the attenuation of the inflammatory response. It is not known to what extent these proinflammatory gene expression changes

studies have demonstrated an effect on suppression of COX-2 expression. Thus, apigenin, genistein, and kaempferol strongly inhibited COX-2 induction in LPS-stimulated macrophages [54]. Other experiments using the gene-reporter assay to express COX-2 showed that some

Several studies have shown that some avonoids inhibit NO production in response to inflammatory stimuli [85]. Hämmäinen et al. compared the effects of a series of avonoid classes containing the most effective compounds were iso avones and avonols. They identified eight compounds as being able to inhibit LPS-induced iNOS expression: avones, daidzein, genistein, isorhamnetin, kaempferol, quercetin, naringenin and pelargonidin [101].

Cellular mechanisms of avonoids modulating gene expression have been actively studied. The most prominent keys of cellular regulation affected by avonoids are the various protein kinases involved in signal transduction 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- $\kappa$ B or activator protein-1 (AP-1) is regulated, and the expression rate of the gene target is controlled [102].

Mitogen-activated protein kinases (MAPKs) are a family of serine/threonine kinases, which connect inflammatory and other extracellular signals to intracellular responses, such as gene expression [102].

The three better characterized MAPKs are extracellular signal-regulated kinase 1 and 2 (Erk1/2), p38, and c-Jun N-terminal kinase (JNK) [103]. P38-MAPK positively regulates a number of cytokine genes in vitro including TNF- $\alpha$ , IL-6 and iNOS [104, 105].

such as gene expression [102]. The three better characterized MAPKs are extracellular signal-regulated kinase 1 and 2 (Erk1/2), p38, and c-Jun N-terminal kinase (JNK) [103].

P38-MAPK positively regulates a number of cytokine genes in vitro including TNF- $\alpha$ , IL-6 and iNOS [104, 105].

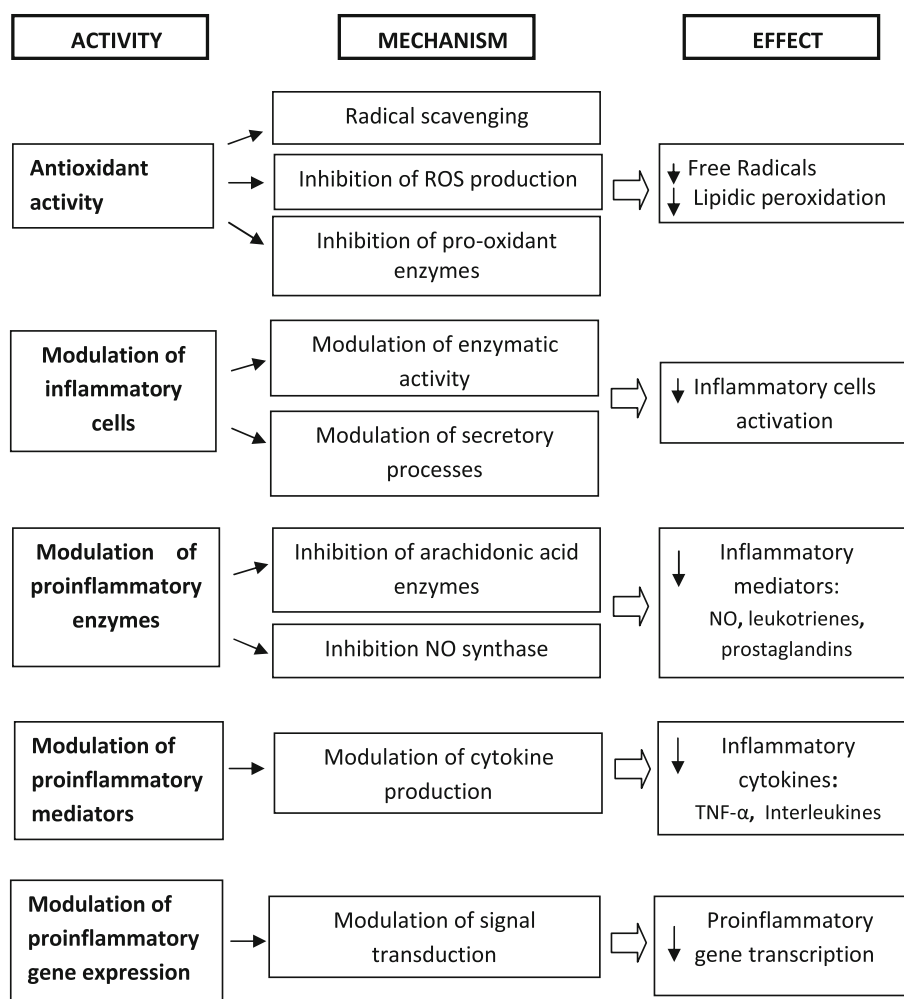
Cytokine production (TNF $\alpha$ , IL-6, IL-10 and IL-1R epithelial and dendritic cells, luteolin blocks LPS-induced antagonist) is strongly inhibited by the administration of aNF- $\kappa$ B signaling and proinflammatory gene expression p38 MAPK inhibitor in vivo, during human endotoxemia through the inhibition of IKK activity [119]. It has been [106]. In human chondrocytes, inhibition of JNK, p38, and reported in mouse alveolar macrophages that luteolin Erk1/2 MAP kinases downregulates IL-1-induced COX-2inhibits LPS-induced in inflammatory reactions by blocking expression and PGE<sub>2</sub>production [107]. Inhibition of the NF- $\kappa$ B and AP-1 activation pathways [10]. MAPKs is likely to result in a suppression of inflammatory Hämäläinen et al. studied the effect of eight flavonoid mediators and these kinases may be a target for anti-inflammatory compounds on the activation of inflammatory transcriptional factors NF- $\kappa$ B and STAT-1. All of them inhibited LPS has been shown to activate MAPK signaling cascadesPS-induced NF- $\kappa$ B activation, but only four of them: [108]. Xagorari et al. [109] have shown that the exposure of genistein, kaempferol, quercetin and daidzein also inhibited RAW 264.7 macrophages to LPS caused phosphorylation of STAT-1 activation. Interestingly, the three most potent ERK1/2, p38, and JNK pathways, pretreatment of cells with antagonists of iNOS expression and NO production (genistein abolished the LPS-induced stimulation of ERK1/2, kaempferol and quercetin) inhibit both NF- $\kappa$ B and p38, but not JNK phosphorylation. The contribution of STAT-1 activations, whereas those flavonoids inhibiting ERK1/2 and p38 pathways in stimulated TNF $\alpha$  production only NF- $\kappa$ B had smaller effect on iNOS expression [10]. In macrophages depends on the origin of macrophages and the nature of the stimulus [110–113]. By using specific inhibitors, these researchers demonstrated that only simultaneous inhibition of the two pathways resulted in drastic reduction of TNF $\alpha$  release [109], which is in agreement with results obtained with alveolar macrophages, where the activation of both ERK and p38 is necessary for optimal TNF $\alpha$  production [114]. Similar results have been obtained with quercetin, where pretreatment of LPS-stimulated RAW 264.7 cells with quercetin inhibited ERK and p38 in using these substances for the treatment of such diseases. activation, but not JNK activation [95].

Another control point of gene expression is the NF- $\kappa$ B transcriptional system, which is a major effector pathway involved in inflammation and innate immune responses. Cancer is a hyperproliferative disorder that involves morphological cellular transformation, dysregulation of inflammatory responses are regulated at the level of transcription by NF- $\kappa$ B. Activation of this nuclear factor is regulated by its endogenous inhibitor I $\kappa$ B, which complexes and sequesters NF- $\kappa$ B in the cytoplasm. Following stimulation, the successive activation of various kinases leads to the phosphorylation and degradation of I $\kappa$ B and subsequent release of NF- $\kappa$ B, which then translocates to the nucleus and activates the transcription of multiple genes, including TNF $\alpha$ , IL-6, IL-8, and other chemokines; MHC class II; ICAM-1; iNOS, and COX-2 [116]. Several flavonoids have been shown to downregulate the production of inflammatory mediators through the blockade of NF- $\kappa$ B pathway at different levels.

In this context, luteolin has shown potent anti-inflammatory properties by inhibiting LPS-induced pro-inflammatory molecule expression both in vitro [117] and in vivo [118]. The molecular mechanisms of luteolin-mediated immunomodulation have been extensively studied in different cellular lines. In murine macrophages RAW 264.7, luteolin inhibits gene expression and proinflammatory cytokine production by blocking protein tyrosine phosphorylation and NF- $\kappa$ B activation [93]. In intestinal

Flavonoids, in inflammation and disease  
Excessive inflammation is considered to be a critical factor in many human diseases, including cancer, cardiovascular diseases, obesity, type II diabetes, or inflammatory bowel disease [97]. The reported anti-inflammatory properties of natural products such as flavonoids may be a crucial factor in using these substances for the treatment of such diseases.  
Flavonoids, in inflammation and cancer  
Cancer is a hyperproliferative disorder that involves morphological cellular transformation, dysregulation of inflammatory responses are regulated at the level of transcription by NF- $\kappa$ B. Activation of this nuclear factor is regulated by its endogenous inhibitor I $\kappa$ B, which complexes and sequesters NF- $\kappa$ B in the cytoplasm. Following stimulation, the successive activation of various kinases leads to the phosphorylation and degradation of I $\kappa$ B and subsequent release of NF- $\kappa$ B, which then translocates to the nucleus and activates the transcription of multiple genes, including TNF $\alpha$ , IL-6, IL-8, and other chemokines; MHC class II; ICAM-1; iNOS, and COX-2 [116]. Several flavonoids have been shown to downregulate the production of inflammatory mediators through the blockade of NF- $\kappa$ B pathway at different levels.  
Inflammation plays a role in malignant processes: chronic inflammation predispose to cancer, immune inflammatory cells and inflammatory mediators are found in cancer, deletion of inflammatory mediators inhibits development of experimental cancers, and long-term use of nonsteroidal anti-inflammatory agents reduces the risk of some tumors  
Inflammation is involved in tumor initiation, promotion and progression [121]. Recent data from mouse models of human cancer have established that inflammation, which orchestrates the tumor microenvironment, is a critical component of tumor evolution [126, 127]. Moreover, excessively and chronically produced proinflammatory mediators are thought to contribute to tumor promotion and progression [121, 126].  
Chronically activated immune cells promote cancer development via direct and indirect mechanisms. Multiple

Fig. 1 Anti-inflammatory mechanisms of flavonoids



mechanisms have been identified explaining the way by which the cellular signaling pathways that regulate proliferation, survival and transformation of cells are of particular interest in current cancer research. Many of the molecular

alterations associated with carcinogenesis occur in cell signaling pathways that regulate cell proliferation and differentiation. These pathways include several kinases such as MAPK, and protein kinases (PK), both of them, closely implicated in inflammatory processes. Abnormal activation or silencing of these kinases or their downstream transcription factors can result in uncontrolled cell growth, leading to malignant transformation [41]. Some flavonoids can modulate these pathways, which in turn regulates gene expression and favors the inhibition of carcinogenesis [97].

Several mechanisms of action have been identified for flavonoid chemoprevention, including estrogenic/anti-inflammatory mechanisms implicated in specific flavonoid estrogenic activity, antiproliferation, induction of cell-cycle arrest or apoptosis, prevention of oxidation, induction of detoxification enzymes, regulation of the host immune system, and changes in cellular signaling [140].

Cancer is a largely preventable disease, namely, through an appropriate diet. Actually, since conventional therapeutic and surgical approaches have not been able to control the incidence of most cancer types, there is an



Fig. 2 Mechanisms of cancer promotion and progression by chronic inflammation

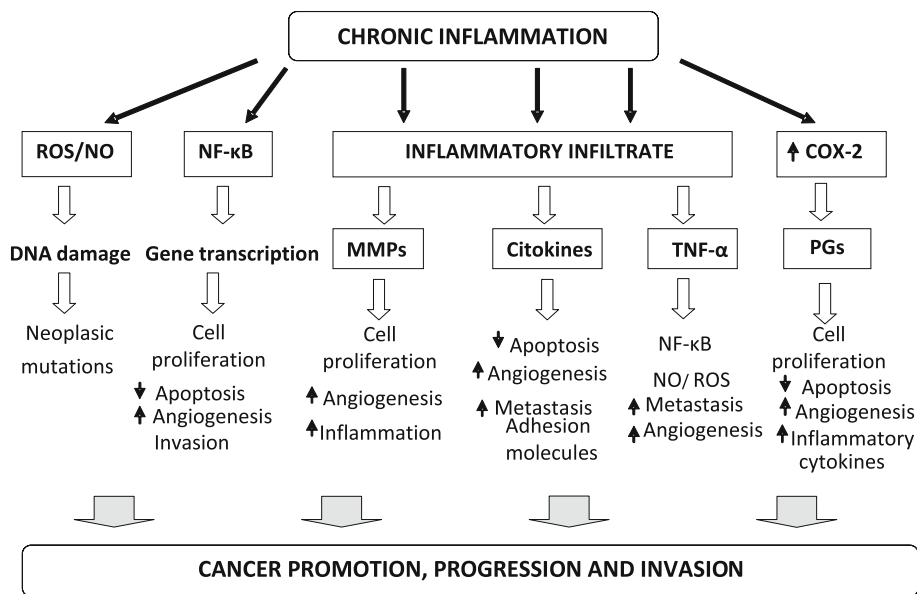


Table 2 Summary of studies demonstrating some of the anti-inflammatory mechanisms implicated in specific flavonoid chemoprevention

Mechanism	Compound	Cancer model	Reference
Antioxidant activity	Quercetin	Lung carcinogenesis	[142]
	Genistein	Neutrophils	[143]
COX-2 inhibition	Naringin	Colon carcinogenesis	[144]
	Tricin	Adenoma in APC <sup>fln</sup> mice	[145]
	Genistein	Human breast cancer cells	[146]
	Apigenin	UVB induced mouse skin tumors	[147]
Inhibition of PKC	Apigenin	Mouse skin tumors	[148]
	Luteolin	Skin tumor cell line	[149]
	Quercetin	Skin tumor cell line	[149]
Modulation of MAPK	Genistein	Prostate cancer	[150]
	Apigenin	Prostate cancer cells	[151]
	Apigenin	Breast carcinoma cells	[152]
Modulation of NFκB	Morin	Different tumor cell lines	[153]
	Genistein	Prostate, breast and pancreatic Cancer cells	[154-156]
	Apigenin	Prostate cancer	[157]

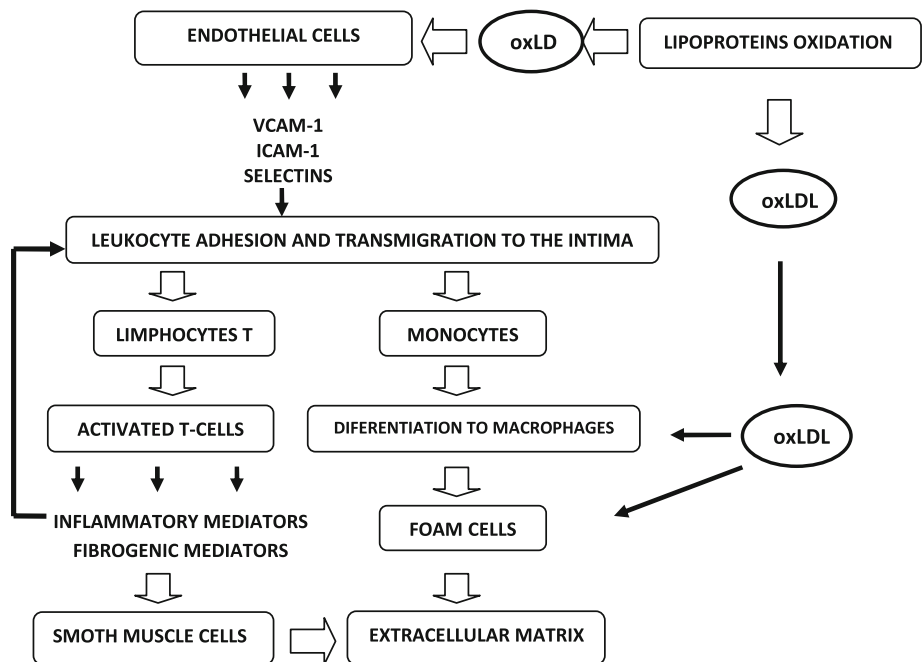
urgent need to develop strategies in order to achieve this goal. In this way, dietary polyphenolic compounds such as flavonoids can be important candidates for chemopreventive agents [158]. However, more data from in-human studies are needed in order to draw definitive conclusions. Recent advances in basic science have established a major role for inflammation in mediating all disease stages from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis [60].

Cardiovascular disease is currently the main cause of death and illness in many countries. In inflammatory processes, initiation of atherosclerosis is the adherence of mononuclear cells to endothelium, which is triggered by a number of adhesion molecules such as P-selectin, E-selectin, and vascular cell adhesion molecule-1 (VCAM-1) and

intercellular adhesion molecule-1 (ICAM-1) [62]. These molecules are expressed by endothelial and/or vascular smooth muscle cells upon proatherogenic stimuli such as oxidized LDL or oxidative free radicals [63, 164]. After monocytes and T lymphocytes bind to the surface of the arterial wall, they migrate into the subendothelial space where they differentiate and are transformed into macrophages and foam cells. Transendothelial migration of leukocytes during the inflammatory process is triggered by chemotactic proteins such as monocyte chemoattractant protein-1 (MCP-1) [65] as well as by proinflammatory cytokines secreted by macrophages and T cells, such as TNF- $\alpha$ , IL-1, IL-6, [166, 167] and growth factors such as platelet derived growth factor (PDGF), basic fibroblast growth factor (bFGF), insulin-like growth factor (IGF) and transforming growth factor- $\beta$  (TGF- $\beta$ ) [168]. These molecules contribute to atherogenesis by maintaining the inflammatory context, dietary antioxidants, as natural anti-inflammatory factors, may produce beneficial cardiovascular effects in human population, as supported by epidemiological data. Several prospective studies have reported inverse associations between antioxidant intake and cardiovascular disease incidence or mortality [174–177], whereas other studies have not [178, 179]. Recently, a prospective study of postmenopausal women showed that dietary intakes of antioxidants were associated with a reduced risk of death due to coronary heart and cardiovascular diseases [180]. In a recent work, Hooper et al. performed a systematic review of the effectiveness of different antioxidant subclasses and

Inflammation is also involved in plaque rupture, which usually occurs in areas of sustained inflammation, and macrophage accumulation. Activated T cells may stimulate matrix metalloproteinases production by macrophages in the lesion. These proteolytic enzymes degrade the collagen protective fibrous cap, rendering the plaque susceptible to rupture [170]. Several cytokines may also upregulate the secretion of TNF- $\alpha$ , IL-1 and MG-CSF, contributing to the instability of the plaque [171]. Moreover, clinical studies have demonstrated systemic markers of inflammation to be strong predictors of clinical events, and specific treatments of atherosclerosis and its risk factor have been associated with reductions in inflammatory markers [172]. This link between inflammation and atherosclerosis provides a new target for future pharmacological agents that may slow the progression of atherosclerosis by inhibiting inflammation [173]. In this context, dietary antioxidants, as natural anti-inflammatory factors, may produce beneficial cardiovascular effects in human population, as supported by epidemiological data. Several prospective studies have reported inverse associations between antioxidant intake and cardiovascular disease incidence or mortality [174–177], whereas other studies have not [178, 179]. Recently, a prospective study of postmenopausal women showed that dietary intakes of antioxidants were associated with a reduced risk of death due to coronary heart and cardiovascular diseases [180]. In a recent work, Hooper et al. performed a systematic review of the effectiveness of different antioxidant subclasses and

Fig. 3 Inflammation in the initiation and progression of atherosclerosis



avonoid-rich food sources on CVD and risk factors. They research have received much attention over the past years concluded that although some avonoid-rich foods mayand a variety of potential beneficial effects have been have some clinically relevant effects on CVD risk factors, elucidated. Their potent anti-inflammatory activity sug- there are limited data from intervention trials for other guests the use of these compounds as potential prophylactic avonoid subclasses consumed as part of a normal diet and therapeutic agents. However, most of the research [181]. In addition to apparent benefits of avonoid intake in involved in in vitro studies and the scarcity of data in the primary prevention, one study suggested that avonoid bioavailability and in vivo models make it difficult to draw intake in the form of tea might have benefit among individuals with established cardiovascular disease [182].

There are several mechanisms by which avonoids may be protective against cardiovascular diseases, including antioxidant, anti-platelet, anti-inflammatory effects as well as increasing HDL, and improving endothelial function. Renewed scientific efforts will provide new insight into Central to the pathogenesis of atherosclerosis is the oxidation of low-density lipoprotein (LDL), avonoids have led to development of a new class of natural anti-oxidant effects and, additionally, some studies have shown that avonoids decrease lipid peroxidation of biological membranes [183]. On the other hand, some mechanisms implicated in the anti-inflammatory effects of avonoids may contribute to its cardiovascular protection, such as regulation of inflammatory mediators production. In an animal model, Droke et al. [184] demonstrated that soy isoflavone administration reduces the risk of cardiovascular disease associated with chronic inflammation, by down-regulating inflammatory mediators such as TNF- $\alpha$  endothelial level. Furthermore, in vitro studies have revealed that dietary avonoids such as apigenin, chrysin, kaempferol or quercetin, attenuate the expression of adhesion molecules in human aortic endothelial cells [185].

Isoflavones also may protect against inflammatory vascular disease by inhibiting monocyte-endothelial cell adhesion [186]. Flavonoids also may contribute to stabilization of the atheroma plaque, quercetin has been shown to be inversely associated with mortality from coronary heart disease by inhibiting the expression of metalloproteinase 1 (MMP1), and the disruption of atherosclerotic plaques [187].

All of these data suggest a great potential for dietary avonoids as natural cardiovascular protectors. Continued studies of the biochemical mechanisms underlying cardiovascular diseases as well as biological effects of avonoids will unveil new strategies for the treatment of such pathological conditions.

## Conclusion

Excessive inflammation is considered as a critical factor in many human diseases, including two of the most extended burdens in the world: cancer and cardiovascular diseases. Epidemiological studies have demonstrated an inverse relationship between dietary avonoid intake and prevalence and risk of these diseases. So that, avonoids

are needed in order to establish their effectiveness in the treatment of chronic diseases such as cancer and cardiovascular diseases.

Central to the pathogenesis of atherosclerosis is the oxidation of low-density lipoprotein (LDL), avonoids have led to development of a new class of natural anti-oxidant effects and, additionally, some studies have shown that avonoids decrease lipid peroxidation of biological membranes [183]. On the other hand, some mechanisms implicated in the anti-inflammatory effects of avonoids may contribute to its cardiovascular protection, such as regulation of inflammatory mediators production. In an animal model, Droke et al. [184] demonstrated that soy isoflavone administration reduces the risk of cardiovascular disease associated with chronic inflammation, by down-regulating inflammatory mediators such as TNF- $\alpha$  endothelial level. Furthermore, in vitro studies have revealed that dietary avonoids such as apigenin, chrysin, kaempferol or quercetin, attenuate the expression of adhesion molecules in human aortic endothelial cells [185].

**Acknowledgments** The authors acknowledge funding from the Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria (INIA) project AT07-003.

## References

1. Nathan C. Points of control in inflammation. *Nature*. 2002;420:846–52.
2. Barton GM. A calculated response: control of inflammation by the innate immune system. *J Clin Invest*. 2008;118:413–20.
3. Haddad PS, Azar GA, Groom S, Boivin M. Natural health products, modulation of immune function and prevention of chronic disease. *Evid Based Complement Alternat Med*. 2005;2:513–20.
4. Yoon J-H, Baek SJ. Molecular targets of dietary polyphenols with anti-inflammatory properties. *Yonsei Med J*. 2005;46:585–96.
5. Robak J, Gryglewski RJ. Bioactivity of avonoids. *Pol J Pharmacol*. 1996;48:555–64.
6. Russo A, Acquaviva R, Campisi A, Sorrenti V, Di Giacomo C, Virgata G, et al. Bio avonoids as antiradicals, antioxidants and DNA cleavage protectors. *Cell Biol Toxicol*. 2000;16:91–8.
7. Havsteen B. The biochemistry and medical significance of the avonoids. *Pharmacol Ther*. 2002;96:67–202.
8. Rotelli AE, Guardia T, Juárez AO, de la Rocha NE. Comparative study of avonoids in experimental models of inflammation. *Pharmacol Res*. 2003;48:601–6.
9. Wang L, Tu YC, Lian TW, Hung JT, Yen JH, Wu MJ. Distinctive antioxidant and anti-inflammatory effects of avonols. *J Agric Food Chem*. 2006;54:9798–804.
10. Bazzano LA, He J, Ogden LG, Loria CM, Vupputuri S, Myers L, et al. Fruit and vegetable intake and risk of cardiovascular disease in US adults: the first National Health and Nutrition Examination Survey Epidemiologic follow-up study. *Am J Clin Nutr*. 2002;76:93–9.
11. Joshipura KJ, Hu HB, Manson JE, Stampfer MJ, Rimm EB, Speizer FE, et al. The effect of fruit and vegetable intake on risk for coronary heart disease. *Ann Intern Med*. 2001;134:1106–14.
12. Liu S, Manson JE, Lee I-M, Cole SR, Hennekens CH, Willett WC, et al. Fruit and vegetable intake and risk of cardiovascular disease: the Women's Health Study. *Am J Clin Nutr*. 2000;72:922–8.
13. Gandini S, Merzenich H, Robertson C, Boyle P. Meta-analysis of studies on breast cancer risk and diet: the role of fruit and

- vegetable consumption and the intake of associated micronutrients. *Eur J Cancer*. 2000;36:636–46.
14. Kolonel LN, Hankin J, Whittemore AS, Wu AH, Gallagher RP, Wilkens L, et al. Vegetables, fruits, legumes and prostate cancer: a multiethnic case-control study. *Cancer Epidemiol Biomark Prev*. 2000;9:795–804.
  15. Feskanich D, Ziegler RG, Michaud DS, Giovannucci EL, Speizer FE, Willett WC, et al. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. *J Natl Cancer Inst*. 2000;92:1812–23.
  16. Jiang F, Dusting GJ. Natural phenolic compounds as cardiovascular therapeutics: potential role of their anti-inflammatory effects. *Curr Vasc Pharmacol*. 2003;1:135–56.
  17. Kim HP, Kun HS, Chang HW, Kang SS. Anti-inflammatory plant flavonoids and cellular action mechanisms. *J Pharmacol Sci*. 2004;96:229–45.
  18. Beecher GR. Overview of dietary flavonoids: nomenclature, occurrence and intake. *J Nutr*. 2003;133:3248S–54S.
  19. Paradkar PN, Blum PS, Berhow MA, Bauman H, Kuo SM. Dietary flavonoids suppress endotoxin-induced inflammatory reaction in liver and intestine. *Cancer Lett*. 2004;215:21–8.
  20. Duan W, Kuo C, Selvarajan S, Chua KY, Bay BH, Wong WS. Anti-inflammatory effects of genistein, a tyrosine kinase inhibitor, on a guinea pig model of asthma. *Am J Respir Crit Care Med*. 2003;167:185–92.
  21. Ruetten HT. Effects of typhostins and genistein on the circulatory failure and organ dysfunction caused by endotoxin in the rat: a possible role for protein tyrosine kinase. *Br J Pharmacol*. 1997;122:59–70.
  22. Verdrengh M, Jonsson IM, Holmdahl R, Tarkowski A. Genistein as an anti-inflammatory agent. *Inflamm Res*. 2003;52:341–6.
  23. Guardia T, Rotelli AE, Juárez AO, Pelzer LE. Anti-inflammatory properties of plant flavonoids. Effects of rutin, quercetin and hesperidin on adjuvant arthritis in rat. *Farmacol*. 2001;56:683–7.
  24. Nishikawa M. Reactive oxygen species in tumor metastasis. *Cancer Lett*. 2008;266:53–9.
  25. Willcox JK, Ash SL, Catignani GL. Antioxidants and prevention of chronic disease. *Crit Rev Food Sci Nutr*. 2004;44:275–95.
  26. Halliwell B. Reactive oxygen species in living systems: source, biochemistry, and role in human disease. *Am J Med*. 1991;91:14S–22S.
  27. Sies H. Oxidative stress: from basic research to clinical application. *Am J Med*. 1991;91:31S–8S.
  28. de Groot H, Rauert U. Tissue injury by reactive oxygen species and the protective effects of flavonoids. *Fundam Clin Pharmacol*. 1998;12:249–55.
  29. Fantone JC, Ward PA. Role of oxygen-derived free-radicals and metabolites in leukocyte-dependent inflammatory reactions. *Am J Pathol*. 1982;107:395–418.
  30. Hart BA, Ram T, Vai Ching IP, Van DI H, Labodie RP. How flavonoids inhibit the generation of luminal-dependent chemiluminescence by activated human neutrophils. *Chem Biol Interact*. 1990;73:323–35.
  31. Limasset B, Le Doucen C, Dore J-C, Ojasoo T, Damon M, De Paulet AC. Effects of flavonoid on the release of reactive oxygen species by stimulated human neutrophils. Multivariate analysis of structure activity relationships (SAR). *Biochem Pharmacol*. 1993;46:1257–71.
  32. Jung HA, Jung MJ, Kim JY, Chung HY, Choi JS. Inhibitory activity of flavonoids from *Prunus davidiana* and other flavonoids on total ROS and hydroxyl radical generation. *Arch Pharm Res*. 2003;26:809–15.
  33. Korkina LG, Afanas'ev IB. Antioxidant and chelating properties of flavonoids. *Adv Pharmacol*. 1997;38:151–63.
  34. Haenen GR, Paquay JB, Korthouwer RE, Bast A. Peroxynitrite scavenging by flavonoids. *Biochem Biophys Res Commun*. 1997;236:591–3.
  35. Lai HH, Yen GC. Inhibitory effect of flavonoids on peroxynitrite-mediated low density lipoprotein oxidation. *Biosci Biotechnol Biochem*. 2002;66:22–8.
  36. Hanaski Y, Ogawa S, Fukui S. The correlation between active oxygen scavenging and antioxidative effects of flavonoids. *Free Radic Biol Med*. 1994;16:845–50.
  37. Keery NL, Abbey M. Red wine and fractionated phenolic compounds prepared from red wine inhibit low density lipoprotein oxidation in vitro. *Atherosclerosis*. 1997;135:93–102.
  38. Shutenko Z, Henry Y, Pinard E, Seylaz J, Potier P, Berthet F, et al. Influence of the antioxidant quercetin in vivo on the level of nitric oxide determined by electron paramagnetic resonance in rat brain during global ischemia and reperfusion. *Biochem Pharmacol*. 1999;57:199–208.
  39. Van Acker SA, Tromp MN, Haenen GR, Van der Vijgh WJ, Bast A. Flavonoids as scavengers of nitric oxide radical. *Biochem Biophys Res Commun*. 1995;214:755–9.
  40. Yen GC, Lai HH. Inhibition of reactive nitrogen species effects in vitro and in vivo by flavonoids and soy-based food extracts. *J Agric Food Chem*. 2003;51:7892–900.
  41. Sarkar A, Bhaduri A. Black tea is a powerful chemopreventor of reactive oxygen and nitrogen species: comparison with its individual constituents and green tea. *Biochem Biophys Res Commun*. 2001;284:173–8.
  42. Chan MM, Fong D, Ho CT, Huang HT. Inhibition of inducible nitric oxide synthase gene expression and enzyme activity by epigallocatechin gallate, a natural product from green tea. *Biochem Pharmacol*. 1997;54:1281–6.
  43. Hong J, Smith TJ, Ho CT, August DA, Yang CS. Effects of purified green and black tea polyphenols on cyclooxygenase and lipoxygenase-dependent metabolism of arachidonic acid in human colon mucosa and colon tumor tissues. *Biochem Pharmacol*. 2001;62:1175–83.
  44. Agarwal SK, Agarwal R, Wood GS, Mukhtar H. Protection against ultraviolet B radiation induced effects in the skin of SKH-1 hairless mice by a polyphenolic fraction isolated from green tea. *Photochem Photobiol*. 1993;58:695–700.
  45. Laughton MJ, Evans PJ, Moroney MA, Hoult JR, Halliwell B. Inhibition of mammalian 5-lipoxygenase and cyclooxygenase by flavonoids and phenolic dietary additives. Relationship to antioxidant activity to iron-reducing ability. *Biochem Pharmacol*. 1991;42:1673–81.
  46. Nagao A, Seki M, Kobayashi H. Inhibition of xanthine oxidase by flavonoids. *Biosci Biotechnol Biochem*. 1999;63:1787–90.
  47. Jolly CA. Diet manipulation and prevention of aging, cancer and autoimmune disease. *Curr Opin Clin Nutr Metab Care*. 2005;8:382–7.
  48. Hance KW, Rogers CJ, Hursting SD, Greiner JW. Combination of physical activity, nutrition, or other metabolic factors and vaccine response. *Front Biosci*. 2007;12:4997–5029.
  49. Volman JJ, Ramakers JD, Plat J. Dietary modulation of immune function by beta-glucans. *Physiol Behav*. 2008;94:276–84.
  50. Middleton E, Kandaswami C, Theoharides TC. The effects of plant flavonoids on mammalian cells: implications for inflammation, heart disease and cancer. *Pharmacol Rev*. 2000;52:673–751.
  51. Rudd CE. CD4, CD8 and the TCR-CD3 complex: a novel class of protein-tyrosine kinase receptor. *Immunol Today*. 1990;11:400–6.
  52. Mustelin T, Abraham RT, Rudd CE, Alonso A, Merlo JJ. Protein tyrosine phosphorylation in T cell signaling. *Front Biosci*. 2002;1:918–69.

53. Campbell M-A, Sefton CM. Protein tyrosine phosphorylation is induced in murine B lymphocytes in response to stimulation with anti-immunoglobulin. *EMBO J*. 1990;9:2125–31.
54. Geng JY, Zhang B, Lotz M. Protein tyrosine kinase activation is required for lipopolysaccharide induction of cytokines in human blood monocytes. *J Immunol*. 1993;151:6692–700.
55. Akiyama T, Ishida J, Nakagawa S, Ogawara H, Wanatabe S, Itoh N, et al. Genistein, a specific inhibitor of tyrosine-specific protein kinases. *J Biol Chem*. 1987;262:5592–5.
56. Trevillyan JM, Lu YL, Atluru D, Phillips CA, Bjorn Dahl JM. Differential inhibition of T cell receptor signal transduction and early activation events by selective inhibitor of protein-tyrosine kinase. *J Immunol* 1990;145.
57. Shapira L, Takashiba S, Champagne C, Amar S, Van Dyke TE. Involvement of protein kinase C and protein tyrosine kinase in lipopolysaccharide-induced TNF-alpha and IL-1 beta production by human monocytes. *J Immunol*. 1994;153:1818–24.
58. Atluru D, Jackson TM, Atluru S. Genistein, a selective protein tyrosine kinase inhibitor, inhibits interleukin-2 and leukotriene B4 production from human mononuclear cells. *Clin Immunol Immunopathol*. 1991;59:379–87.
59. Comalada M, Ballester I, Bañón E, Sierra S, Xaus J, Cuez J, et al. Inhibition of pro-inflammatory markers in primary bone marrow-derived mouse macrophages by naturally occurring flavonoids: analysis of the structure-activity relationship. *Biochem Pharmacol*. 2006;72:1010–21.
60. Bennet JP, Gomperst BD, Wollenweber E. Inhibitory effects of natural flavonoids on secretion from mast cells and neutrophils. *Arzneimittelforschung*. 1981;31:433–7.
61. Berton G, Schneider C, Romeo D. Inhibition by quercetin of activation of polymorphonuclear leukocyte functions. Stimulus-specific effects. *Biochim Biophys Acta*. 1980;595:47–55.
62. Kanashiro A, Souza JG, Kabeya LM, Azzolini AE, Lucisano-Valim YM. Elastase release by stimulated neutrophils inhibited by flavonoids: importance of the catechol group. *Z Naturforsch* 2007;62.
63. Selloum L, Bouriche H, Tigrine C, Boudoukha C. Anti-inflammatory effect of rutin on rat paw oedema, and on neutrophils chemotaxis and degranulation. *Exp Toxicol Pathol*. 2003;54:313–8.
64. Tordera M, Fernández ML, Alcaraz MJ. 1994. Influence of anti-inflammatory flavonoids on degranulation and arachidonic acid release in rat neutrophils. *Z Naturforsch [C]*. 49:235–40.
65. Chang HW, Baek SH, Chung KW, Son KH, Kim HP, Kang SS. Inactivation of phospholipase A<sub>2</sub> by naturally occurring flavonoid, ochna avone. *Biochem Biophys Res Commun*. 1994;205:843–9.
66. Gil B, Sanz MJ, Terencio MC, Giunasegaran R, Playa M, Alcaraz MJ. Morello avone, a novel flavonoid inhibitor of human secretory phospholipase A<sub>2</sub> with anti-inflammatory activity. *Biochem Pharmacol*. 1997;53:733–40.
67. Chi YS, Jong HG, Son KH, Chang HW, Kang SS, Kim HP. Effects of naturally prenylated flavonoids on enzymes metabolizing arachidonic acid: cyclooxygenases and lipoxygenases. *Biochem Pharmacol*. 2001;62:1185–91.
68. Kobuchi H, Virgili F, Packer L. Assay of inducible form of nitric oxide synthase activity: effect of flavonoids and plant extracts. *Methods Enzymol*. 1999;301:504–13.
69. Cheon BS, Kim YH, Son KS, Chang HW, Kang SS, Kim HP. Effects of prenylated flavonoids and flavonoids on lipopolysaccharide-induced nitric oxide production from the mouse macrophage cell line RAW 264.7. *Planta Med* 2000; 66:596–600.
70. Lee T-P, Matteliano ML, Middleton E. Effect of quercetin on human polymorphonuclear leukocyte lysosomal enzyme release and phospholipid metabolism. *Life Sci*. 1982;31:2765–74.
71. Lanni C, Becker EL. Inhibition of neutrophil phospholipase A<sub>2</sub> by *p*-bromophenylacetyl bromide, nordihydroguaiaretic acid, 5,8,11,14-eicosatetraenoic acid and quercetin. *Inst Archs Allergy Appl Immunol*. 1985;76:214–7.
72. Lindahl M, Tagesson C. Selective inhibition of group II phospholipase A<sub>2</sub> by quercetin. *Inflammation*. 1993;17:573–82.
73. Süleyman H, Demircan B, Karagöy. Anti-inflammatory and side effects of cyclooxygenase inhibitors. *Pharmacol Rep*. 2007;59:247–58.
74. Khanapure SP, Garvey DS, Janero DR, Letts LG. Eicosanoids in inflammation: biosynthesis, pharmacology, and therapeutic frontiers. *Curr Top Med Chem*. 2007;7:311–40.
75. Kuhn H. Biologic relevance of lipoxygenase isoforms in atherogenesis. *Expert Rev Cardiovasc Ther*. 2005;3:1099–110.
76. Bauman J, von Bruchhausen FV, Wurm G. Flavonoids and related compounds as inhibitors of arachidonic acid peroxidation. *Prostaglandins*. 1980;20:627–39.
77. Landor R, Mower RL, Steiner M. Modification of platelet function and arachidonic acid metabolism by flavonoids. Structure-activity relations. *Biochem Pharmacol*. 1984;33:1525–30.
78. Wakabayashi I, Yasui K. Wogonin inhibits inducible prostaglandin E<sub>2</sub> production in macrophages. *Eur J Pharmacol*. 2000;406:477–81.
79. Chi YS, Cheon BS, Kim HP. Effect of wogonin, a plant flavone from *Scutellaria radix*, on the suppression of cyclooxygenase-2 and the induction of inducible nitric oxide synthase in lipopolysaccharide-treated RAW 264.7 cells. *Biochem Pharmacol* 2001; 61:1195–203.
80. You KM, Jong HG, Kim HP. Inhibition of cyclooxygenase/lipoxygenase from human platelets by polyhydroxylated/methoxylated flavonoids isolated from medicinal plants. *Arch Pharm Res*. 1999;22:18–24.
81. Chung CP, Park JB, Bae KH. Pharmacological effects of methanolic extract from root of *Scutellaria baicalensis* and its flavonoids on human gingival fibroblasts. *Planta Med*. 1995;61:150–3.
82. Mashsha HG, Singh SA, Rao AR. Inhibition of lipoxygenase by soy isoflavones: Evidence of isoflavones as redox inhibitors. *Arch Biochem Biophys*. 2007;461:176–85.
83. Hong J, Bose M, Ju J, Ryu JH, Chen X, Sang S, et al. Modulation of arachidonic acid metabolism by curcumin and related beta-diketone derivatives: effects on cytosolic phospholipase A<sub>2</sub>, cyclooxygenases and 5-lipoxygenase. *Carcinogenesis*. 2004;25:1671–9.
84. Moncada S, Palmer MJ, Higgs DA. Nitric oxide: physiology, pathophysiology, and pharmacology. *Pharmacol Rev*. 1992;43:109–42.
85. Liang YC, Huang YT, Tsai SH, Lin-Shiau SY, Chen CF, Lin JK. 1999. Suppression of inducible cyclooxygenase and inducible nitric oxide synthase by apigenin and related flavonoids in mouse macrophages. *Carcinogenesis*. 20:1945–52.
86. Autore G, Rastrelli L, Lauro MR, Marzocco S, Sorrentino R, Pinto A, et al. Inhibition of nitric oxide synthase expression by a methanolic extract of *Crescencia alata* and its derived flavonols. *Life Sci*. 2001;70:523–34.
87. Kim HK, Cheon BS, Kim YH, Kim SY, Kim HP. Effects of naturally occurring flavonoids on nitric oxide production in the macrophage cell line RAW 264.7 and their structure-activity relationships. *Biochem Pharmacol* 1999;58.
88. Raso GM, Meli R, Di Carlo G, Pacilio M, Di Carlo R. Inhibition of inducible nitric oxide synthase and cyclooxygenase-2 expression by flavonoids in macrophage J774A.1. *Life Sci* 2001; 68:921–31.
89. Sheu F, Lai HH, Yen GC. Suppression of effect of soy isoflavones on nitric oxide production in RAW 264.7 macrophages. *J Agric Food Chem*. 2001;49:1767–72.

90. Chen YC, Shen SC, Lee WR, Hou WC, Yang LL, Lee TJ. Inhibition of nitric oxide synthase inhibitors and lipopolysaccharide induced inducible NOS and cyclooxygenase-2 gene expression by rutin, quercetin, and quercetin pentaacetate in RAW 264.7 macrophages. *J Cell Biochem.* 2001;82:537–48.
91. Chen XW, FGraner SC, Anderson JJ. Iso avones regulate interleukin-6 and osteoprotegerin synthesis during osteoblast cell differentiation via an estrogen-receptor-dependent pathway. *Biochem Biophys Res Commun.* 2002;295:417–22.
92. Ding SZ, Cho CH, Lam SK. Regulation of interleukin-6 production in a human gastric epithelial cell line MKN-28. *Cytokine.* 2000;12:1129–35.
93. Xagorari A, Papapetropoulos A, Mauromatis A, Economou M, Fostis T, Roussos C. Luteolin inhibits an endotoxin-stimulated phosphorylation cascade and proinflammatory cytokine production in macrophages. *J Pharmacol Exp Therap.* 2001;296:181–7.
94. Cho JY, Kim PS, Park JB, Yoo ES, Baik KU, Kim YK, et al. Inhibitor of tumor necrosis factor- $\alpha$  production in lipopolysaccharide-stimulated RAW264.7 cells from *Morpha fruticosa*. *J Ethnopharmacol.* 2000;70:127–33.
95. Cho SY, Park SJ, Kwon MJ, Jeong TS, Bok SH, Choi WY, et al. Quercetin suppresses proinflammatory cytokines production through MAP kinases and NF- $\kappa$ B pathway in lipopolysaccharide-stimulated macrophage. *Mol Cell Biochem.* 2003;243:153–60.
96. Van Dien M, Takahashi K, Mu MM, Koide N, Sugiyama T, Mori I, et al. Protective effect of wogonin on endotoxin-induced lethal shock in D-galactosamine-sensitized mice. *Microbiol Immunol.* 2001;45:751–6.
97. Santangelo C, Vari R, Scazzocchio B, Di Benedetto R, Filesi C, Masella R. Polyphenols, intracellular signalling and in ammation. *Ann Ist Super Sanita.* 2007;43:394–405.
98. Mutoh M, Takahashi M, Fukuda K, Komatsu H, Enya T, Matsushima-Hibiya Y, et al. Suppression by avonoids of cyclooxygenase-2 promoter-dependent transcriptional activity in colon cancer cells: structure–activity relationship. *Jpn J Cancer Res.* 2000;91:686–91.
99. Hooshmand S, Soung do Y, Lucas EA, Madhally SV, Levenson CW, Arjmandi BH. Genistein reduces the production of proinflammatory molecules in human chondrocytes. *J Nutr Biochem.* 2007; 18:609–14.
100. Chen CY, Peng WH, Tsai KD, Hsu SL. Luteolin suppresses in ammation-associated gene expression by blocking NF- $\kappa$ B and AP-1 activation pathway in mouse alveolar macrophages. *Life Sci.* 2007;81:1602–14.
101. Hämäläinen M, Nieminen R, Vuorela P, Heinonen M, Moilanen E. Anti-inflammatory effects of avonoids: genistein, kaempferol, quercetin, and daidzein inhibit STAT-1 and NF- $\kappa$ B activations, whereas avone, isorhamnetin, naringenin, and pelargonidin inhibit only NF- $\kappa$ B activation along with their inhibitory effect on iNOS expression and NO production in activated macrophages. *Mediat In amm.* 2007; 2007:45673.
102. Su B, Karin M. Mitogen-activated protein kinase cascades and regulation of gene expression. *Curr Opin Immunol.* 1996;8:402–11.
103. Dong C, Davis RJ, Flavell RA. MAP kinases in the immune response. *Annu Rev Immunol.* 2002;20:55–72.
104. Herlaar E, Brown Z. MAPK signaling cascades in inflammatory disease. *Mol Med Today.* 1999;5:439–47.
105. Ono K, Han J. The p38 signal transduction pathway: activation and function. *Cell Signal.* 2000;12:1–13.
106. Branger J, van den Blink B, Weijer S, Madwed J, Bos CL, Gupta A, et al. The p38 signal transduction pathway: activation and function. *J Immunol.* 2002;168:4070–7.
107. Nieminen R, Leinonen S, Lahti A, Vuolteenaho K, Jalonen U, Kankaanranta H, et al. Inhibitors of mitogen-activated protein kinases downregulate COX-2 expression in human chondrocytes. *Mediat In amm.* 2005;5:249–55.
108. Feng GJ, Goodridge HS, Harnett MM, Wei SQ, Nikolaev AV, Higson AP, et al. Extracellular signal-related kinase (ERK) and p38 mitogen-activated protein (MAP) kinases differentially regulate the lipopolysaccharide-mediated induction of inducible nitric oxide synthase and IL-12 in macrophages: Leishmania phosphoglycans subvert macrophage IL-12 production by targeting ERK MAP kinase. *J Immunol.* 1999; 163:6403–6412.
109. Xagorari A, Roussos C, Papapetropoulos A. Inhibition of LPS-stimulated pathways in macrophages by the avonoid luteolin. *Br J Pharmacol.* 2002;136:1058–64.
110. Means TK, Pavlovich RP, Roca D, Vermuelen MW, Fenton MJ. Activation of TNF- $\alpha$  transcription utilizes distinct MAP kinase pathways in different macrophage populations. *J Leuk Biol.* 2000;67:885–93.
111. Baldassare JJ, Bi Y, Bellone CJ. The role of p38 mitogen-activated protein kinase in IL-1 beta transcription. *J Immunol.* 1999;162:5367–73.
112. van den Blink B, Juffermans NP, ten Hove T, Schultz MJ, van Deventer SJ, van der Poll T, et al. p38 mitogen-activated protein kinase inhibition increases cytokine release by macrophages in vitro and during infection in vivo. *J Immunol.* 2001;166:582–7.
113. Kontoyiannis D, Pasparakis M, Pizarro TT, Cominelli F, Kollias G. Impaired on/off regulation of TNF biosynthesis in mice lacking TNF AU-rich elements: implications for joint and gut associated immunopathologies. *Immunity.* 1999;10:387–98.
114. Carter AB, Monick MM, Hunninghake GW. Both Erk and p38 kinases are necessary for cytokine gene transcription. *Am J Resp Cell Mol Biol.* 1999;20:751–8.
115. Pereira SG, Oakley F. Nuclear factor- $\kappa$ B1: regulation and function. *Int J Biochem Cell Biol.* 2008;40:1425–30.
116. Barnes PJ, Karin M. Nuclear factor- $\kappa$ B: a pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med.* 1997;336:1066–71.
117. Park E, Kum S, Wang C, Park SY, Kim BS, Schuller-Levis G. Anti-inflammatory activity of herbal medicines: inhibition of nitric oxide production and tumor necrosis factor- $\alpha$  secretion in an activated macrophage-like cell line. *Am J Chin Med.* 2005;33:415–24.
118. Kotanidou A, Xagorari A, Bagli E, Kitsanta P, Fostis T, Papapetropoulos A, et al. Luteolin reduces lipopolysaccharide-induced lethal toxicity and expression of proinflammatory molecules in mice. *Am J Resp Crit Care Med.* 2002;165:818–23.
119. Kim JS, Jobin C. The avonoid luteolin prevents lipopolysaccharide-induced NK- $\kappa$ B signaling and gene expression by blocking I- $\kappa$ B kinase activity in intestinal epithelial cells and bone-marrow derived dendritic cells. *Immunology.* 2005;115:373–87.
120. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell.* 2000;100:57–70.
121. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002;420:860–7.
122. Shacter E, Weitzman SA. Chronic inflammation and cancer. *Oncology.* 2002;16:217–26.
123. Fox JG, Wang TC. Inflammation, atrophy and gastric cancer. *J Clin Invest.* 2007;117:60–9.
124. Dobrovolskaia MA, Kozlov SV. Inflammation and cancer: when NF- $\kappa$ B amalgamates the perilous partnership. *Curr Cancer Drug Targets.* 2005;5:325–544.
125. YC Xiao H. Combination regimen with statins and NSAIDs: a promising strategy for cancer chemoprevention. *Int J Cancer.* 2008;123:983–90.

126. Balkwill F, Charles KA, Mantovani A. Smoldering and polarized inflammation in the initiation and promotion of malignant disease. *Cancer cell*. 2005;7:211–7.
127. de Visser KE, Coussens LM. The inflammatory tumor microenvironment and its impact on cancer development. *Contrib Microbiol*. 2006;13:118–37.
128. Rivoli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. *Am J Clin Nutr*. 2003;78:559S–69S.
129. Vainio H, Weiderpass E. Fruit and vegetables in cancer prevention. *Nutr Cancer*. 2006;54:111–42.
130. Yang CS, Landau JM, Huang MT, Newmark HL. Inhibition of carcinogenesis by dietary polyphenolic compounds. *Annu Rev Nutr*. 2001;21:381–406.
131. Le Marchand L. Cancer preventive effects of flavonoids—a review. *Biomed Pharmacother*. 2002;56:269–301.
132. Wang ZY, Huang HT, Lou YR, Xie JG, Reuhl KR, Newmark HL, et al. Inhibitory effects of black tea, green tea, decaffeinated black tea, and decaffeinated green tea on ultraviolet B light-induced skin carcinogenesis in 7,12-dimethylbenz(a)anthracene-initiated SKH-1 mice. *Cancer Res*. 1994;52:1162–70.
133. Lu YP, Lou YR, Lin Y, Shih WJ, Huang MT, Yang CS, et al. Inhibitory effects of orally administered green tea, black tea, and caffeine on skin carcinogenesis in mice previously treated with ultraviolet light (light-risk mice): relationship to decreased tissue fat. *Cancer Res*. 2001;61:5002–9.
134. Yamane T, Hagiwara N, Tateishi M, Akachi S, Kim M, Okuzumi J, et al. Inhibition of azoxymethane-induced colon carcinogenesis in rat by green tea polyphenol fraction. *Jpn J Cancer Res*. 1991;82:1336–9.
135. Kawabata K, Tanaka T, Honjo S, Kakumoto M, Hara A, Makita H, et al. Chemopreventive effects of dietary flavonoid morin on chemically induced rat tongue carcinogenesis. *Int J Cancer*. 1999;83:381–6.
136. Deschner EE, Ruperto J, Wong G, Newmark HL. Quercetin and rutin as inhibitors of azoxymethanol-induced colonic neoplasia. *Carcinogenesis*. 1991;12:1193–6.
137. Messina MJ, Persky V, Setchell KD, Barnes S. Soy intake and cancer risk: a review of the in vitro and in vivo data. *Nutr Cancer*. 1994;21:113–31.
138. Wietrzyk J, Opolski A, Madej J, Radzikowski C. Antitumor and antimetastatic effect of genistein alone or combined with cyclophosphamide in mice transplanted with various tumors depends on the route of tumor transplantation. *In Vivo*. 2000;14:357–62.
139. Pollard M, Suckow MA. Dietary prevention of hormone refractory prostate cancer in Loblund–Wistar rats: a review of studies in a relevant animal model. *Comp Med*. 2006;56:461–7.
140. Birt DF, Hendrich S, Wang W. Dietary agents in cancer prevention: flavonoids and iso flavonoids. *Pharmacol Therapeutics*. 2001;90:157–77.
141. Fresco P, Borges F, Diniz C, Marques MPM. New insights on the anticancer properties of dietary polyphenols. *Med Res Rev*. 2006;26:747–66.
142. Kamaraj S, Vinodh Kumar R, Anandakumar P, Jagan S, Ramakrishnan G, Devaki T. The effects of quercetin on antioxidant status and tumor markers in the lung and serum of mice treated with benzo(a)pyrene. *Biol Pharm Bull*. 2007;30:2268–73.
143. D'Alessandro TL, Prasain J, Benton MR, Botting N, Moore R, Darley-Usmar V, et al. Polyphenols, inflammatory response, and cancer prevention: chlorination of iso flavones by human neutrophils. *J Nutr*. 2003;133:3773S–7S.
144. Vanamala J, Leonardi T, Patil BS, Taddeo SS, Murphy ME, Pike LM, et al. Suppression of colon carcinogenesis by bioactive compounds in grapefruit. *Carcinogenesis*. 2006;27:1257–65.
145. Cai H, Al-Fayez M, Tunstall RG, Platten S, Greaves P, Steward WP, et al. The rice bran constituent tricin potentially inhibits cyclooxygenase enzymes and interferes with intestinal carcinogenesis in *Apc<sup>Min</sup>* mice. *Mol Cancer Ther*. 2005;4:1287–92.
146. Horia E, Watkins BA. Complementary actions of docosahexaenoic acid and genistein on COX-2, PGE<sub>2</sub> and invasiveness in MDA-MB-231 breast cancer cells. *Carcinogenesis*. 2007;28:809–15.
147. Van Dross RT, Hong X, Essengue S, Fischer SM, Pelling JC. Modulation of UVB-induced and basal cyclooxygenase-2 (COX-2) expression by apigenin in mouse keratinocytes: role of USF transcription factors. *Mol Carcinog*. 2007;46:303–14.
148. Lin JK, Chen YC, Huang YT, Lin-Shiau SY. Suppression of protein kinase C and nuclear oncogene expression as possible molecular mechanisms of cancer chemoprevention by apigenin and curcumin. *J Cell Biochem*. 1997;Suppl 28–29:39–48.
149. Lee LT, Huang YT, Hwang JJ, Lee PP, Ke FC, Nair MP, et al. Blockade of the epidermal growth factor receptor tyrosine kinase activity by quercetin and luteolin leads to growth inhibition and apoptosis of pancreatic tumor cells. *Anticancer Res*. 2002;22:1615–27.
150. Khan N, Afaq F, Mukhtar H. Cancer chemoprevention through dietary antioxidants: progress and promise. *Antioxid Redox Signal*. 2008;10:475–510.
151. Shukla S, Gupta S. Apigenin-induced cell cycle arrest is mediated by modulation of MAPK, PI3K-Akt, and loss of cyclin D1 associated retinoblastoma dephosphorylation in human prostate cancer cells. *Cell cycle*. 2007;6:1102–14.
152. Yin F, Giuliano AE, Law RE, Van Herle AJ. Apigenin inhibits growth and induces G2/M arrest by modulating cyclin-CDK regulators and ERK MAP kinase activation in breast carcinoma cells. *Anticancer Res*. 2001;21:413–20.
153. Manna SK, Aggarwal RS, Sethi G, Aggarwal BB, Ramesh GT. Morin (3,5,7,2,4'-pentahydroxy flavone) abolishes nuclear factor-kappa B activation induced by various carcinogens and inflammatory stimuli, leading to suppression of nuclear factor-kappaB-regulated gene expression and up-regulation of apoptosis. *Clin Cancer Res*. 2007;8:2290–7.
154. Li Y, Sarkar FH. Inhibition of nuclear factor kappaB activation in PC3 cells by genistein is mediated via Akt signaling pathway. *Clin Cancer Res*. 2002;8:2369–77.
155. Davis JN, Kucuk O, Sarkar FH. Genistein inhibits NF-kappaB activation in prostate cancer cells. *Nutr Cancer*. 1999;35:167–74.
156. Rahman KW, Li Y, Sarkar FH. Inactivation of Akt and NF-kappaB play important roles during indole-3-carbinol-induced apoptosis in breast cancer cells. *Nutr Cancer*. 2004;48:84–94.
157. Shukla S, Gupta S. Suppression of constitutive and tumor necrosis factor alpha-induced nuclear factor (NF)-kappaB activation and induction of apoptosis by apigenin in human prostate carcinoma PC-3 cells: correlation with down-regulation of NF-kappaB-responsive genes. *Clin Cancer Res*. 2004;10:3169–78.
158. Kelloff GJ. Perspectives on cancer chemoprevention research and drug development. *Adv Cancer Res*. 2000;78:199–334.
159. Libby P. Inflammation and atherosclerosis. *Nature*. 2002;420:868–74.
160. Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation*. 2002;105:1135–43.
161. Dong ZM, Chapman SM, Brown AA, Frenette PS, Hynes RO, Wagner DD. The combined role of P- and E-selectins in atherosclerosis. *J Clin Invest*. 1998;102:145–52.
162. Libby P. Changing concepts of atherogenesis. *J Intern Med*. 2000;247:349–58.
163. Bonomini F, Tengattin IS, Fabiano A, Bianchi R, Rezzani R. Atherosclerosis and oxidative stress. *Histol Histopathol*. 2008;23:381–90.

164. Hofnagel O, Luechtenborg B, Weissen-Plenz G, Robenek H177. Yochum L, Kushi LH, Meyer K, Folsom AR. Dietary avonoid Statins and foam cell formation: impact on LDL oxidation and uptake of oxidized lipoproteins via scavenger receptors. *Biochim Biophys Acta*. 2007;1771:1117–24.
165. Charo IF, Taubman MB. Chemokines in the pathogenesis of vascular disease. *Circ Res*. 2004;95:858–66.
166. Szekanez Z. Pro-inflammatory cytokines in atherosclerosis. *Isr Med Assoc J*. 2008;10:529–30.
167. Ohsuzu F. The roles of cytokines, inflammation and immunity in vascular diseases. *J Atheroscler Thromb*. 2004;11:313–21.
168. Mallat Z, Gojova A, Marchiol-Fournigault C, Esposito B, Kamaté C, Merval R, et al. Inhibition of transforming growth factor-beta signaling accelerates atherosclerosis and induces an unstable plaque phenotype in mice. *Circ Res*. 2001;89:930–4.
169. Kapronis EA, Liapis CD, Kakisis JD, Dimitroulis D, Papavasiliou VG. Inflammation and atherosclerosis. *Eur J Vasc Endovasc Surg* 2006;31.
170. Schonbeck U, Mach F, Sukhova GK, Murphy C, Bonnefoy JY, Fabunmi RP, et al. Regulation of matrix metalloproteinase expression in human vascular smooth muscle cells by T lymphocytes: a role for CD40 signaling in plaque rupture? *Circ Res*. 1997;81:448–54.
171. Wu L, Fan J, Matsumoto S, Watanabe T. Induction and regulation of matrix metalloproteinase-12 by cytokines and CD40 signaling in monocyte/macrophages. *Biochem Biophys Res Commun*. 2000;269:808–15.
172. Zebrack JS, Anderson JL. Role of inflammation in cardiovascular disease: how to use C-reactive protein in clinical practice. *Prog Cardiovasc Nurs*. 2002;17:174–85.
173. Shishehbor MH, Bhatt DL. Inflammation and atherosclerosis. *Curr Atheroscler Rep*. 2004;6:131–9.
174. Hertog MGL, Kromhout D, Aravanis C, Blackburn H, Buzina R, Fidanza F, et al. Flavonoid intake and long-term risk of coronary heart disease and cancer in the seven countries study. *Arch Intern Med*. 1995;155:381–6.
175. Knekt P, Jarvinen R, Reunanen A, Maatela J. Flavonoid intake and coronary mortality in Finland: a cohort study. *BMJ*. 1996;312:478–81.
176. Knekt P, Kumpulainen J, Jarvinen R, Rissanen H, Hänninen M, Reunanen A, et al. Flavonoid intake and risk of chronic diseases. *Am J Clin Nutr*. 2002;76:560–8.
177. Yochum L, Kushi LH, Meyer K, Folsom AR. Dietary avonoid intake and risk of cardiovascular disease in postmenopausal women. *Am J Epidemiol*. 1999;149:943–9.
178. Rimm E, Katan M, Ascherio A, Stampfer MJ, Willett WC. Relation between intake of avonoids and risk for coronary heart disease in male health professionals. *Ann Intern Med*. 1996;125:384–9.
179. Sesso HD, Gaziano JM, Liu S, Buring JE. Flavonoid intake and the risk of cardiovascular disease in women. *Am J Clin Nutr*. 2003;77:1400–8.
180. Mink PJ, Scrafford CG, Barraj LM, Harnack L, Hong CP, Nettleton JA, et al. Flavonoid intake and cardiovascular disease mortality: a prospective study in postmenopausal women. *Am J Clin Nutr*. 2007;85:895–909.
181. Hooper L, Kroon PA, Rimm EB, Cohn JS, Harvey I, Le Cornu KA, et al. Flavonoids, avonoid-rich foods, and cardiovascular risk: a meta-analysis of randomized controlled trials. *Am J Clin Nutr*. 2008;88:38–50.
182. Mukamal KJ, Maclure M, Muller JE, Sherwood JB, Mittleman MA. Tea consumption and mortality after acute myocardial infarction. *Circulation*. 2002;105:2476–81.
183. Wiswedel I, Hirsch D, Kropf S, Gruening M, Pster E, Schewe T, et al. Flavanol-rich cocoa drink lowers plasma F(2)-isoprostane concentrations in humans. *Free Radic Biol Med*. 2004;37:411–21.
184. Droke EA, Hager KA, Lerner MR, Lightfoot SA, Stoecker BJ, Brackett DJ, et al. Soy isoflavone averts chronic inflammation-induced bone loss and vascular disease. *J Inflamm* 2007;4:17.
185. Lotito SB, Frei B. Dietary avonoids attenuate tumor necrosis factor alpha-induced adhesion molecule expression in human aortic endothelial cells. Structure–function relationships and activity after pass metabolism. *J Biol Chem*. 2006;281:37102–10.
186. Chacko BK, Chandler RT, D'Alessandro TL, Mundhekar A, Khoo NKH, Botting N, et al. Anti-inflammatory effects of isoflavones are dependent on low and human endothelial cell PPAR-gamma. *J Nutr*. 2007;137:351–6.
187. Osiecki H. The role of chronic inflammation in cardiovascular disease and its regulation by nutrients. *Altern Med Rev*. 2004;9:32–53.