Phenolic compounds: Natural alternative in inflammation treatment. A Review

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Abstract: Inflammation is a biological defense mechanism caused by the interruption of the tissue homeostasis caused by the presence of a biological, chemical, or physical agents in the body; immune system produces a series of pro-inflammatory mediators, however their overproduction, as occurs in chronic inflammation, might lead to the occurrence of several chronic diseases. For this reason, slowing down the inflammation process becomes very important, and with this purpose non-steroid anti-inflammatory drugs are generally used with the subsequent occurrence of adverse side effects. As an alternative in inflammation treatment, folklore medicine has used several plants and herbs with minimal or null side effects, with the phenolic compounds being one of their principal components. Phenolic compounds are able to inhibit either the production or the action of pro-inflammatory mediators, resulting in anti-inflammatory capacity.

Subjects: Complementary & Alternative Medicine; Food Chemistry; Nutraceuticals & Functional Foods; Nutrition; Pharmaceutical Medicine

Keywords: inflammation; anti-inflammatory capacity; phenolic compounds

1. Introduction
Inflammation is a biological reaction caused by the disruption of the tissue homeostasis, occurring in response to the presence of a biological, chemical, or physical agent in the body (Medzhitov, 2008). Some of these agents may be pathogens (bacteria, fungi, and viruses), trauma (shock or burns), toxic compounds (pollutants), as well as reactions of the immune system (hypersensitivity) (Ashley, Weil, & Nelson, 2012).

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PUBLIC INTEREST STATEMENT
Inflammation is associated with chronic diseases; phenolic compounds can slow down this process with minimal or null adverse side effects. This review describes the inflammation process and treatment and focuses on mode of action of anti-inflammatory properties of phenolic compounds. The present review is a comprehensive study that collects informative knowledge which may be of interest to researchers, scientists, and pharmacists.
Inflammation can be acute or chronic, depending on the type of stimulus and the efficiency of the reaction to remove such stimulus or injured tissues. Acute inflammation begins quickly (within minutes) and lasts a few hours or a few days, characterized by the exudation of fluid and plasma proteins and leukocyte emigration (mainly neutrophils). When immune system successfully eliminates damaging agents in acute inflammation, the reaction disappears, but if the response fails to remove them, it can cause a chronic phase. Chronic inflammation is associated with the presence of lymphocytes and macrophages, vascular proliferation, fibrosis, and tissue destruction (Kumar, Abbas, Fausto, & Mitchell, 2012).

During inflammation, some cells, mainly macrophages, promote the production of pro-inflammatory mediators. These mediators include interleukin (IL)-1β, IL-6, IL-8, among others; tumor necrosis factor (TNF)-α, reactive oxygen species (ROS), nitric oxide (NO), and prostaglandins (PGs).

Overproduction of these mediators in chronic inflammation has been linked to the onset of chronic degenerative diseases such as arthritis, atherosclerosis, asthma, Alzheimer’s, cancer, among others (Rock & Kono, 2008). For this reason, slowing down the inflammation process became very important, with this purpose non-steroid anti-inflammatory drugs (NSAIDs) are generally used. Nevertheless, the use of NSAIDs has many side effects, such as gastrointestinal disorders, water retention, renal failure, bronchospasm, and hypersensitivity reactions (Hawkey & Langman, 2003; Tamblyn et al., 1997).

As an alternative in inflammation treatment, folklore medicine has used several plants and herbs with minimal or null side effects. Phenolic compounds, have attracted research attention by being one of the principal components responsible for their anti-inflammatory capacity.

2. Inflammatory process
During inflammation, macrophage cells could be activated through the recognition of a pathogen endotoxin, lipopolysaccharide (LPS), by the macrophages toll-like receptor (TLR). This event triggers a signaling pathway that will release the NF-κB (Nuclear factor kappa-light-chain-enhancer of activated B cells), a transcription factor that is responsible for the activation of genes associated with the transcription of inflammatory mediators, such as such as interleukins, TNF-α and PGs, and inflammatory enzymes, such as inducible nitric oxide synthase (iNOS) responsible for the synthesis of NO and cyclooxygenases (COXs). TLR signaling pathway also triggers the generation of reactive oxygen species (ROS) (Friedman & Hughes, 2002; Kumar et al., 2012; Proell, Riedl, Fritz, Rojas, & Schwarzenbacher, 2008; Rock & Kono, 2008). Overproduction of these mediators, as occurs in chronic inflammation, might lead to the occurrence of several chronic diseases.

3. Oxidative stress and inflammation
Oxidative stress is the result of the chemical imbalance between antioxidants and pro-oxidants leading to damaging effects. Epidemiological and experimental evidence has shown that oxidative stress is closely related to chronic diseases such as cancer, diabetes, Alzheimer’s disease, Parkinson’s disease, and inflammation (Cataldi, 2010; Emerit, Edeas, & Bricaire, 2004; Mohamed, 2014; Odendaal and Schauss (2014); Sies, 1997; Valko et al., 2007).

Pro-oxidants (also called oxidants) are formed as a normal product of the mitochondrial respiratory chain. In normal conditions, oxidants are eliminated by antioxidant protective mechanisms; on the other hand, under pathophysiological conditions they can be produced at elevated rates (Sies, 1997). Overproduction of oxidants can result in the formation of ROS that may cause somatic mutations, leading to neoplastic transformation (Sies, 1997; Siti, Kamisah, & Kamsiah, 2015).

ROS are among the most important physiologically produced oxidants, and they are formed as byproducts of the mitochondrial respiratory chain. The most important ROS are superoxide (O2·−), peroxynitrite (ONOO−), hydrogen peroxide (H2O2), and nitric oxide (NO•). If superoxide and nitric
oxide react, they form the highly reactive peroxynitrite, which is an important mediator of lipid peroxidation and protein nitration, including oxidation of LDL (Griendling & FitzGerald, 2003). ROS have been related to inflammation and the further development of atherosclerosis. In this sense, inflammation and nitric oxide production play an important role in the development of the atherosclerotic plaque (Selmi, Cocchi, Lanfredini, Keen, & Gershwin, 2008). Consequently, it is of human health concern to find ways to prevent/treat inflammation before it develops into a chronic disease.

4. Inflammation and their relationship with chronic diseases

4.1. Neurodegenerative diseases
The progressive dysfunction and loss of neurons in the central nervous system is known as neurodegeneration, and represents the major cause of cognitive and motor dysfunction. Commonly, when we refer to neurodegenerative diseases we relate the term to Alzheimer’s and Parkinson’s diseases, however neurodegeneration is also observed in neurotrophic infections, traumatic brain and spinal cord injury, stroke, neoplastic disorders, multiple sclerosis, and amyotrophic lateral sclerosis, as well as neuropsychiatric disorders and genetic disorders. All these disorders present chronic microglia activation (macrophages from central nervous system), which can trigger neurotoxic pathways, leading to progressive degeneration (Amor et al., 2014). Inflammatory responses related to neurodegeneration include augmented expression of cytokines, adhesion molecules, degradative enzymes, increased generation of ROS accompanied by prominent cellular activation of microglia (Walker, Whetzel, & Lue, 2015).

Increased inflammatory response and greater oxidative stress burden are two of the main pathogenic mechanisms responsible for neurodegenerative diseases. The elevation of IL-1β, as well as IL-6 and TNF-α, is broadly recognized as a critical factor of neuroinflammation (Azizi et al., 2015). For example, it has been mentioned that levels of the inflammatory cytokine IL-1β are increased in brain tissue, cerebrospinal fluid, and blood/serum from Alzheimer’s disease patients (Das, 2011). Moreover, IL-1β and TNF-α are strong stimuli for iNOS expression which synthetize NO. It has been demonstrated that high levels of NO is associated with the increase in TNF-α levels in patients in the severe stages of Alzheimer’s disease (Belkhelfa et al., 2014).

4.2. Cardiovascular disease
Cardiovascular disease (CVD) is a chronic inflammatory condition with immune competent cells in lesions producing mainly pro-inflammatory cytokines. CVD is considered as the major cause of death in developed countries, and it is also an important cause of morbidity worldwide. The major direct cause of CVD is atherosclerosis due to the rupture of atherosclerotic plaques. It was recently understood that inflammation plays a key role in atherosclerosis development, from the initial lesion to the end-stage thrombotic complications. Nowadays, anti-inflammatory treatments are evaluated as novel treatments for CVD (Frostegård, 2013).

Typically, endothelial cells (ECs), which form the innermost surface of the artery wall, resist adhesion by leukocytes. However, atherosclerosis’s triggers (smoking, hypertension, hyperglycemia, obesity or insulin resistance) can initiate the expression of adhesion molecules by ECs, thus allowing the attachment of leukocytes to the arterial wall. After that, pro-inflammatory cytokines such as interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) provide a chemotactic stimulus for adherent leukocytes to migrate into the intima. Later during lesion evolution, lymphocytes and macrophages secrete cytokines and growth factors that can promote the migration and proliferation of smooth muscle cells, the cytokine interferon-γ inhibit the production of collagen by smooth muscle cells and cytokine IL-1 stimulates macrophages to express collagen-degrading enzymes. The lack of collagen weakens the fibrous cap that protects the blood from the thrombogenic lipid core of the plaque. When the plaque ruptures, a thrombus is formed; this is responsible for most of the acute complications of atherosclerosis (Libby, 2006).
4.3. Arthritis
Arthritis is a chronic inflammatory disease considered as an autoimmune disease with unknown etiology in which systemic overproduction of pro-inflammatory cytokines such as IL-6 and TNF-α may accelerate cardiovascular complications. Arthritis affects approximately 0.5–1% of the worldwide population and it commonly results in detriment of the quality of life of the patients (Quan, Thiele, Tian, & Wang, 2008).

A distinctive symptom of arthritis is the synovial inflammation and its severity may vary with disease progression. Synovial inflammation spreads systemically and transforms into chronic inflammation manifested by increased cytokine release and abnormally high levels of C-reactive protein, connecting arthritis with cardiovascular complications through inflammation (Riegsecker, Wiczynski, Kaplan, & Ahmed, 2013).

4.4. Cancer
Cancer is a very complex disease produced by cells that have lost their usual control over growth (Pal et al., 2014). It has been mentioned that a poor resolution of inflammation and an unchecked inflammatory reaction can induce chronic inflammation, predisposing the host to various diseases, including cancer (Wu, Antony, Meitzler, & Doroshow, 2014). For instance, there is evidence which proves that pro-inflammatory cytokines, namely TNF- and IL-6, induce breast cancer cell growth and tumor formation, and induce adhesive recruitment of metastatic breast cancer cells on E-selectin coated surfaces under flow (Bhatelia, Singh, & Singh, 2014; Geng et al., 2013).

5. Treatment for inflammation

5.1. Conventional treatment: NSAIDs
Currently, NSAIDs are some of the most commonly used drugs in the world for the treatment of numerous conditions that involve inflammation. According to a survey of medication use in the USA, more than 37% of adults consumed NSAID at least once a week (Kaufman et al., 2002). Up to 2010, the USA generated about 70 million prescriptions of NSAID annually. In recent years, the market has been growing, in 2010, the NSAIDs industry was valued at 355 billion US dollars and over 6 billion worldwide (Chaudhari, 2011).

NSAIDs drugs can be non-selective, meaning they act by inhibiting prostaglandin synthase isoenzymes COX-1 and COX-2, either by covalently modifying the enzyme or by competing with the substrate for the active site (Williams, Mann, & DuBois, 1999).

The long-term use of NSAIDs shows both therapeutic and adverse side effects, mostly because the decrease in COX-1 prostaglandin production. The principal side effects are gastrointestinal disorders, generally moderate and reversible, although some patients can suffer from severe peptic ulcer, intestinal bleeding, and perforation of the digestive tract, damage on the small intestine, and distal. In the USA, 7,600 deaths and 76,000 hospitalizations have occurred related to the use of NSAIDs (Tamblyn et al., 1997). Meanwhile in the UK, NSAIDs are reported to cause annually approximately 3,500 hospitalizations and 400 deaths just from ulcer bleeding in 60-year-old people and above (Hawkey & Langman, 2003). In addition to gastrointestinal effects, NSAIDs might cause salt and water retention, renal failure, bronchospasm, and hypersensitivity reactions (Hawkey & Langman, 2003).

As previously mentioned, COX 2 is over expressed at sites of inflammation. Therefore, there are COX-2 selective drug inhibitors (known as coxibs), these present similar anti-inflammatory efficacy with the advantage of less gastrointestinal side effects than non-selective drugs (Bombardier et al., 2000; Vane, 1994). Nevertheless, they are related to enhancing renal sodium reabsorption, thus predisposing to hypertension and edema; this phenomenon is associated with cardiovascular diseases (Hawkey & Langman, 2003).
5.2. Alternative treatment: natural sources

Because of the adverse side effects of NSAIDs, traditional medicines and natural products used in folklore medicine have been studied as potential alternatives to these drugs; these having minimal toxicity related to the gastrointestinal tract.

In this sense, some of the studies focused on anti-inflammatory alternatives are exposed below:

In folklore medicine, *Artemisia herba alba* and *Magnolia officinalis* are widely used for their multiple beneficial bioactivities, such as their anti-inflammatory properties. According to Messaoudene et al. (2011), this anti-inflammatory effect is due to the inhibition and the stimulation of the production of cytokines IL-12 and of IL-4, respectively, in addition to the decrease in NO.

In Mexican folklore medicine some herbal infusions are used, recently a study has stated that salvillia (*Buddleia scordioides*), chamomile (*Chamaemelum nobile*), and laurel (*Listea glaucescens*) had a positive effect over pro-inflammatory markers, relieving oxidative stress and downregulating COX-2, TNFα, NF-κB, and IL-8 (Herrera-Carrera et al., 2015).

Recent studies have documented that supplementation with pomegranate fruit extract inhibits inflammatory symptoms in vivo. According to Shukla et al. (2008) this anti-inflammatory effect is achieved by the inhibition of the inflammatory cytokine-induced production of PGE2, and NO. Other natural NO-inhibitors are the methanolic extracts of green and red Kohlrabi cultivars, which inhibited LPS-induced NO production in a dose-dependent manner by the suppression of iNOS and COX-2 production (Jung et al., 2014).

*Smallanthus sonchifolius* (Poepp.) H. Rob., Asteraceae, known as yacon, is an herb that is traditionally used for the treatment of diabetes in folk medicine. However, recent studies have demonstrated that yacon leaves have anti-inflammatory capacity because of the presence of chlorogenic acid and NO, TNF-α and PGE2 inhibition (Oliveira et al., 2013).

*C. ternatea* L. (Leguminosae), also known by the common name “butterfly pea,” is traditionally used in Southeast Asia for its anti-inflammatory and analgesic properties. Recently, it has been proved that *C. ternatea* polyphenols have anti-inflammatory properties in lipopolysaccharide (LPS)-induced inflammation in RAW 264.7 macrophage cells with distinct molecular targets (Nair, Bang, Schreckinger, Andarwulan, & Cisneros-Zevallos, 2015).

On the other hand, it has been proposed that the concentration and time of exposure are determining factors in the safety of consuming certain natural compounds (García-Mediavilla et al., 2007); this is the case of curcumin, which may exhibit both antioxidant and pro-oxidant activities. It is possible that these opposing activities of curcumin are regulated by the concentration when the effect of curcumin may switch from antioxidant to pro-oxidant (Aggarwal & Harikumar, 2009); this may also have an effect on the switch from anti-inflammatory to pro-inflammatory.

The search for natural anti-inflammatory agents with fewer side effects has made the leap from research laboratories to pharmaceutical industry. For example, Unigen Pharmaceuticals, Inc. patented a mixture of free-B-ring flavonoids and flavans isolated from the Scutellaria and the Acacia genus of plants, respectively. The active compounds are found to be effective by simultaneously inhibiting both the COX-2 and arachidonate 5-lipoxygenase (5-LO) enzymes. They recommend the new drug for the relief from joint discomfort and pain associated with conditions such as osteoarthritis, rheumatoid arthritis, and other injuries that result from overuse of joints. The compounds cited in the invention demonstrated similar effectiveness on pain relief, better effectiveness at decreasing stiffness, and noticeable improvement in physical function compared to the prescription drug Celebrex™ (Pfizer, Inc.) in clinical studies (Jia, 2006). Moreover, other nutraceutic preparation has been patented, which is a mixture of compounds, and one among them is 3,4',5 trihydroxy stilbene or resveratrol. According to the inventors, this mixture has anti-inflammatory properties and
they recommend its use in the treatment of inflammatory diseases such as rheumatoid arthritis, spondyloarthitis, Crohn’s disease, osteoarthritis, arthropathies, and also neurodegenerative diseases (Burcelin & Seree, 2011).

Even though plant-derived preparations have been used in folklore medicine for hundreds of years, recently herbal medications (as supplements and therapy adjuvants) are more common because of their relatively few side effects. However, the obtaining and preparation processes are not standardized yet, and therefore, many factors such as the extraction process, the ripening, or the cultivars used may affect the true concentration of the product. Because of this, the governmental agencies, like the FDA, routinely inspect the manufacture and claims of supplements (Maroon, Bost, & Maroon, 2010).

6. Phenolic compounds and inflammation

Phenolics are a heterogenic group of compounds derived from the secondary metabolism of plants. Structurally, phenolic compounds have at least one aromatic ring to which one or more hydroxyl groups are bonded to aromatic or aliphatic structures. Phenolic compounds can be grouped into flavonoids and non-flavonoids (Bravo, 1998).

(1) Flavonoids are composed of two aromatic rings linked through an oxygen heterocycle. Depending on the degree of hydrogenation and the replacement of the heterocycle they can be subclassified as flavonols, flavones, isoflavones, anthocyanins, flavanols, flavanones, etc. Flavonoids usually occur in nature as glycosides (Figure 1).

(2) Non-flavonoids. Benzoic and cinnamic acid are two of the most representative compounds of this kind, and they are commonly known as phenolic acids (Figure 2). Some other common phenolic acids are stilbenes, tannins, and lignins.

In recent years, phenolic compounds have been of increasing interest to science and food industry for their beneficial health effects. Epidemiological data have related a high intake of phenolic-rich
food to a decreased rate of chronic diseases such as diabetes, cardiovascular diseases, Alzheimer’s disease, Parkinson’s disease, and inflammation (Bravo, 1998; Mohamed, 2014). Phenolic compounds are thought to be responsible, at least in part, for this beneficial effect.

As it was described above, chronic and acute inflammation processes are implicated in the development of chronic diseases. Therefore, interventions that modify the inflammatory cascade associated with diseases may be regarded as potential targets in the prevention of such conditions (Allgrove & Davison, 2014; Mao et al., 2000; Selmi et al., 2008).

In this sense, some phenolic compounds have exhibited anti-inflammatory properties. Although the precise mechanisms of this anti-inflammatory activity are not fully elucidated, there is a correlation between the high intake of food rich in these compounds and a downregulation of the inflammatory response (Alarcón de la Lastra & Villegas, 2005).

The association of phenolic structure and anti-inflammatory activity has been previously discussed, and structural requirements have been established using different targets of inflammation (Gautam & Jachak, 2009; Lago et al., 2014):

1. A planar ring system is essential in the flavonoid molecules to exhibit the activity.
2. Unsaturation in the C ring as ketonic carbonyl at C4 and/or C2-C3 double bond.
3. Hydroxyl groups in B ring and at C5 and C7 of A ring are necessary.
4. The number and position of hydroxyl groups as the catechol group at ring B
5. The flavones and flavanols having a hydroxyl group at 4’ position of B ring showed higher activity than those do not.
6. The methylation of the hydroxyl groups at 3, 5, or 4’ positions improved the activity.
7. The methylation of the 3-hydroxyl group reduced the cytotoxicity
8. Flavones exhibited higher activities than the corresponding isoflavones, flavonols, and flavanones.
9. The non-glycosylation of the molecule, aglycones have a bigger effect than glycosides.

On the last one, the role of glycosides is controversial because in some cases, it has been observed that they decrease the anti-inflammatory activity (Kim, Son, Chang, & Kang, 2004) but facilitate absorption (Hollman, de Vries, van Leeuwen, Mengelers, & Katan, 1995). Nevertheless, compounds that do not have these structural features can also exhibit anti-inflammatory activity.

Studies more specific have determined the relationship between phenolic structure and pro-inflammatory mediators. Three main structural characters give rise to flavonoids NO inhibitory potential: (a) a C2-C3 double bond, (b) a bulky group as a substituent lowered or nullify the inhibitory effect of compound (aglycones have bigger effect than glycosides), (c) 7 and 4’ OH-groups, but this last feature should be accompanied by any of the aforementioned (Hämäläinen, Nieminen, Vuorela, Heinonen, & Moilanen, 2007).

In case of prostaglandin production, two important factors have been observed for the high inhibition activities: (a) C2-C3 double bond and (b) 4-oxo functional group of the C ring. Because of these, the flavones and flavanols are considered the most efficient (Takano-Ishikawa, Goto, & Yamaki, 2006).

7. Mode of action of phenolic compounds as anti-inflammatory agents
Phenolic compounds work in a similar way as NSAIDs do, additionally some of them inhibit other pro-inflammatory mediators besides COX by inhibiting their activity or gene expression. Besides, some phenolic compounds can up/downregulate transcriptional factors, like nuclear factor-kB (NF-kB) or Nrf-2, in inflammatory and antioxidant pathways (Maroon et al., 2010; Sergent, Piront, Meurice, Toussaint, & Schneider, 2010).
The structure of phenolic compounds highly influences their mechanisms of anti-inflammatory action. For example, unsaturation in the C ring gives stability to the intermediate radical species by resonance. Besides, a double bond located in C2-C3 induces coplanarity between rings A and C, stimulating the interaction of the flavonoid with the enzymatic active site (Lättig et al., 2007). The catechol group at the B ring helps in enzymatic oxidation, inducing the formation of electrophilic species allowing nucleophilic addition. Finally, ligands of phenolic compounds participate in the formation of covalent bonds between the flavonoids and macromolecules (Lago et al., 2014).

Although the precise mechanisms of this antiinflammatory activity are not fully dilucidated, there is a correlation between the high intake of food rich in these compounds and a downregulation of the inflammatory response (Alarcón de la Lastra & Villegas, 2005). It is has been hypothesized that phenolic compounds exert anti-inflammatory activity by inhibiting the synthesis of pro-inflammatory mediators, modification of eicosanoid synthesis, inhibition of activated immune cells, or inhibition of nitric oxide synthase and xyclooxygenase-2 via its inhibitory effects on nuclear factor NF-κβ (Alarcón de la Lastra & Villegas, 2005; Chuang & McIntosh, 2011; Emerit et al., 2004).

Some dietary flavonoids have shown to modulate inflammation mediators such as IL-6. In this matter, cocoa and tea flavonols, a type of flavonoids, have shown to affect IL-6 concentration in blood plasma in a dose-response way (Stote et al., 2012). Cocoa phenolic compounds have attracted attention due to their health properties. Epidemiological studies have related inflammation and moderate consumption of cocoa products.

Some studies show a positive effect in inhibition of inflammation markers; on the other hand Mathur et al. (2002) reported no effect on intake of cocoa phenolics and inflammation markers (IL-1β, 1L-6, TNF-α), nevertheless a reduction in LDL oxidation was shown, this can led to a decreased vascular inflammation, oxidative stress, reduction of nitric oxide, and prevention of platelet aggregation that translates in prevention of cardiovascular diseases (Allgrove & Davison, 2014; Rodrigo, Miranda, & Vergara, 2011). It is important to remind the reader that even though experimental data are not decisive; epidemiological data show a reduced rate of chronic diseases in people with higher dietary intake of food rich in phenolic compounds. So more research is needed in order to dilucidate the exact mechanisms of actions in which phenolic compounds exert their anti-inflammatory activity.

Also, grapes and red wine consumption have also been the focus of numerous studies on the anti-inflammatory properties of phenolic compounds. In vitro and in vivo studies have been performed using grape phenolic extracts; and it has been reported that procyanidins show inhibition of inflammatory mediators. Results showed decreased in nitric oxide concentration, prostaglandins E2 and ROS. This effect was mainly attributed to the antioxidant properties of phenolic compounds (Chacón et al., 2009; Panico et al., 2006; Rodrigo et al., 2011; Subbaramaiah et al., 1998; Terra et al., 2009).

Several studies have focused on the evaluation of extracts containing a mixture of many compounds. In this sense, every class of phenolics present in the extracts could have a different effect on pro-inflammatory mediators. As we can see in the analysis of C. ternatea phenolic extract, flavonols showed strong inhibition of COX-2 activity and partial ROS suppression, while the ternatin anthocyanins inhibited nuclear NF-κB translocation, iNOS protein expression, and NO production through a non-ROS suppression mechanism (Nair et al., 2015).

The mechanism of action of phenolic compounds is executed by a variety of inhibitory activities of pro-inflammatory mediators and/or gene expression. An individual phenolic compound or a mixture of them can exert anti-inflammatory activity through many ways; while drugs work in a single one (Figure 3). The flavonol kaempferol have shown inhibitory activity of LPS-induced NF-κB activations (Hämäläinen et al., 2007), iNOS expression and NO production (Hämäläinen et al., 2007; Lee, Choi, Choi, Park, & Sung, 2007), COX-2 expression and PGE2 production (Lee et al., 2007; Yoon et al., 2013), aldosterone signaling and aldosterone-induced gene expression (indirect cytokine-inhibition) (Liu,
Xiao, & Fang, 2013), and cytokines (TNF-α, IL-1β) production (Kong, Luo, Li, Zhou, & He, 2013). Table 1 summarizes other studies regarding phenolic compounds mode of anti-inflammatory action.

8. Conclusion
Phenolic compounds are a wide and heterogeneous group, ubiquitous in plant-based foods, and possess a remarkable anti-inflammatory capacity due to their multiple inhibitory activities of pro-inflammatory mediators. This has led researchers to propose dietary phenolic compounds as a potential natural alternative for the treatment of inflammation and related diseases, with minimal or null adverse side effects. Nevertheless, most of these studies have used an in vitro approach with phenolic extracts of different plant sources without considering how human digestion and metabolism could affect the potential anti-inflammatory activity of dietary phenolics. As a result, it has not been possible to understand the precise mechanism and sites in which phenolic compound provide anti-inflammatory activities.
### Table 1. Mode of anti-inflammatory action of dietary phenolic compounds

| Phenolic compound | Type of phenolic | Inhibitory activity (Mechanism of action) | Reference |
|-------------------|------------------|------------------------------------------|-----------|
| Genistein         | Isoflavone       | LPS-induced STAT-1 and NF-κB activations, iNOS expression and NO-production | Choe et al. (2012); García-Mediavilla et al. (2007); Hämäläinen et al. (2007); Lee et al. (2007) |
| Daidzein          | Isoflavone       |                                          |           |
| Quercetin         | Flavonol         |                                          |           |
| Isohamnetin       | Flavonol         | LPS-induced NF-κB activation, iNOS expression, NO-production | Bodet, La, Epifano, and Grenier (2008); Hämäläinen et al. (2007); Jayaraman, Jesudoss, Menon, and Namassivayam (2012); Tsai et al. (2012) |
| Naringenin        | Flavanone        |                                          |           |
| Pelargonidin      | Anthocyanin      |                                          |           |
| Kaempferol        | Flavonol         | LPS-induced STAT-1 and NF-κB activations, iNOS expression and NO-production, COX2 expression, Cytokines TNF-α, IL-1β, IL-6 production | Hämäläinen et al. (2007); Kong et al. (2013); Lee et al. (2007); Liu et al. (2013) |
| Apigenin          | Flavone          | NO-production, COX2 expression and PGE, production, Cytokines TNF-α, IL-1β, IL-6, IL-12 production | Jeong, Lee, Jeong, Kim, and Kim (2009); Lee et al. (2007) |
| Epicatechin       | Flavan-3-ol      | NF-κB activity NO-production, PGE, production, Cytokines TNF-α, IL-6 production | Morrison et al. (2014); Wang and Cao (2014) |

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### Competing interests
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