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PHENOLIC COMPOUNDS AND HUMAN HEALTH BENEFITS

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ABSTRACT

Phenolic compounds are present in all plant organs and are therefore an integral part of the human diet. They have been shown to play important roles in human health. Indeed, high intakes of tea, fruits, vegetables, and whole grains, which are rich in phenolic compounds, have been linked to lowered risks of many chronic diseases, including cancer, cardiovascular diseases, chronic inflammation, and many degenerative diseases. These potential beneficial health effects of phenolic compounds are a resultof their biological properties, including antioxidant, anti-inflammatory, anti-cancer, and antimicrobial activities. In this paper, the mechanisms of the biological actions of phenolic compounds will be presented and discussed.

Keywords: Antioxidant, anticancer, anti-inflammatory, antimicrobial, phenolic compounds.

Các hợp chất phenolic và lợi ích cho sức khỏe con người

TÓM TẮT

Các hợp chất phenolic có mặt trong tất cả các bộ phận của thực vật và từ đó là một phần trong thức ăn của con người. Các hợp chất này đã được chứng minh là đóng vai trò quan trọng đối với sức khỏe. Trên thực tế, việc sử dụng một lượng lớn thực phẩm giàu các hợp chất phenolic như trà, quả, rau và ngũ cốc nguyên hạt gắn với sự giảm nguy cơ mắc nhiều bệnh mãn tính như ung thư, các bệnh tim mạch, viêm mãn tính và nhiều bệnh thoái hóa. Những lợi ích tốt cho sức khỏe con người của các hợp chất phenolic có được nhờ các tính chất sinh học của chúng bao gồm hoạt động kháng oxi hóa, kháng viêm, kháng ung thư và kháng vi sinh vật. Trong bài bao này, cơ chế hoạt động sinh học của các hợp chất phenolic sẽ được giới thiệu và thảo luận.

Từ khóa: Hợp chất phenolic, kháng oxi hóa, kháng ung thư, kháng viêm, kháng vi sinh vật.

1. INTRODUCTION

Phenolic compounds refer to one of the most numerous and widely distributed groups of secondary metabolites in the plant kingdom, with about 10,000 phenolic structures identified to date (Kennedy and Wightman, 2011). Furthermore, they are considered to be the most abundant antioxidants in the human diet (Mudgal *et al*., 2010), and contribute up to 90% of the total antioxidant capacity in most fruits and vegetables.

Phenolic compounds are substances with aromatic ring(s) bearing one or more hydroxyl moieties, either free or involved in ester or ether bonds (Manach *et al*., 2004). They occur primarily in a conjugated form, with one or more sugar residues linked to hydroxyl groups by glycoside bonds. Association with other compounds, such as carboxylic acids, amines, and lipids are also common (Bravo, 1998).

Phenolic compounds have been shown to play important roles in human health. Indeed, epidemiological studies strongly support a role for phenolic compounds in the prevention of many diseasesthat are associated with oxidative stress and chronic inflammation, such as cardiovascular diseases, cancers, osteoporosis,

diabetes mellitus, arthritis, and neurodegenerative diseases (Tsao, 2010; Cicerale *et al.*, 2012). These potential beneficial health effects of phenolic compounds are the resultof their biological properties, including antioxidant, anti-inflammatory, anti-cancer, and antimicrobial activities (Cicerale *et al.*, 2012). All these biological actions of phenolic compounds strongly depend on their chemical structures (D'Archivio *et al.*, 2010). In this paper, firstly, classification of phenolic compounds based on their structure will briefly be mentioned. The mechanisms of biological actions will then be presented and finally, the relationship between the chemical structures and their biological activities will be discussed.

2. CLASSIFICATION OF PHENOLIC COMPOUNDS

Phenolic compounds are divided into different classes (Figure 1) according to the number of phenolic rings they have and the structural elements that link these rings. They include phenolic acids, flavonoids, stilbenes, tannins, and lignans (Manach *et al.*, 2004). Among them, flavonoids are the largest class and can be further subdivided into six major subclasses based the oxidation state of the central heterocycle. They include flavones, flavonols, flavanones, flavanols, anthocyanidins, and isoflavones (Manach *et al.*, 2004).

Tannins also contribute an abundant number of phenolic compounds in the human diet. They give an astringent taste to many edible plants. They are subdivided into two major groups: hydrolysable and condensed tannins (Brano, 1998). Hydrolysable tannins are derivatives of gallic acid, which is esterified to a core polyol, mainly glucose (Bravo, 1998), while condensed tannins are oligomeric and polymeric flavan-3-ols. Condensed tannins are also called proanthocyanidins because an acid-catalysed cleavage of the polymeric chains produces anthocyanidins (Tsao, 2010). Concerning lignans, they are plant products of low molecular weights formed primarily from oxidative coupling of two *p*-propylphenol moieties with the most frequent phenylpropane units called monolignol units, being *p*-coumaryl, coniferyl, and sinapyl alcohols (Cunha *et al.*, 2012).

Phenolic compounds represent a huge family of compounds presenting a very large range of structures. The presentation in detail of all of phenolic group's structures will be the frame of other papers. In this publication, the health-promoting activities of phenolic compounds are the focus.

3. ANTIOXIDANT ACTIVITY

Antioxidant activity is the most studied property of phenolic compounds. Antioxidants, in general, and most phenolic compounds, in particular, can slow down or inhibit the oxidative process generated by ROS (reactive oxygen species) and RNS (reactive nitrogen species) in excess.

ROS and RNS are well recognised as being both deleterious and beneficial species. At low or moderate concentrations, they have physiological roles in cells, for example, in the defence against infectious agents (Valco *et al.*, 2007). Their level is controlled by endogenous antioxidants including enzymes and antioxidant vitamins (*i.e.*, vitamins E and C). However, various agents such as ionising radiation, ultraviolet light, tobacco smoke, ozone, and nitrogen oxides in polluted air can cause "oxidative stress" characterised by an over production of ROS and RNS on one side, and a deficiency of enzymatic and non-enzymatic antioxidants on the other. ROS and RNS in excess can damage cellular lipids, proteins, or DNA, and thereby inhibit their normal functions (Valco *et al.*, 2007).

Phenolic compounds are strong dietary antioxidants that reinforce, together with other dietary components (carotenoids, antioxidant vitamins), our antioxidant system against oxidative stress (Tsao, 2010). The antioxidant mechanisms of phenolic compounds are now well understood (Nijveldt *et al.*, 2001; Amic *et al.*, 2003), and include: (*i*) direct free radical scavenging, (*ii*) chelation with transition metal ions, and (*iii*) inhibition of enzymes,

such as xanthine oxidase, catalysing the radical formation.

Direct free radical scavenging

Phenolic compounds have the ability to act as antioxidants by a free radical scavenging mechanism with the formation of less reactive phenolic radicals. Phenolic compounds (PheOH) inactivate free radicals via hydrogen atom transfers (reaction 1) or single electron transfers (reaction 2) (Leopoldini *et al.*, 2011):

PheOH + R$^{\bullet}$ → PheO$^{\bullet}$ + RH (hydrogen atom transfer - 1)

PheOH + R$^{\bullet}$ → PheOH$^{+\bullet}$ + R^{-} (single electron transfer - 2)

The reactions produce molecules (RH) or anions (R^{-}) with an even number of electrons that are less reactive than the free radicals. PheO$^{\bullet}$subsequently undergoes a change to a resonance structure by redistributing the unpaired electron on the aromatic core. Thus, phenolic radicals exhibit a much lower reactivity compared to the radical R$^{\bullet}$, and are relatively stable due to resonance delocalisation and the lack of suitable sites for attack by molecular oxygen (Leopoldini *et al.*, 2011). In addition, they could react further to form unreactive compounds, probably by radical-radical termination (Amic *et al.*, 2003):

PheO$^{\bullet}$ + R$^{\bullet}$ → PheO-R (radical-radical coupling reaction)

PheO$^{\bullet}$ + PheO$^{\bullet}$ → PheO-OPhe (radical-radical coupling reaction)

Chelation with transition metal ions

The generation of various free radicals is closely linked to the participation of transition metals (Valko *et al.*, 2007). In fact, these metals in their low oxidation state may be involved in Fenton reactions with hydrogen peroxide, from which the very dangerous reactive oxygen species OH$^{\bullet}$ is formed (Leopoldini *et al.*, 2011):

$M^{n+} + H_2O_2 \rightarrow M^{(n+1)+} + {}^{\bullet}OH + OH^{-}$

Phenolic compounds can entrap transition metals by chelation and thereby prevent them from taking part in the reactions generating $^{\bullet}$OH free radicals (Figure 2).

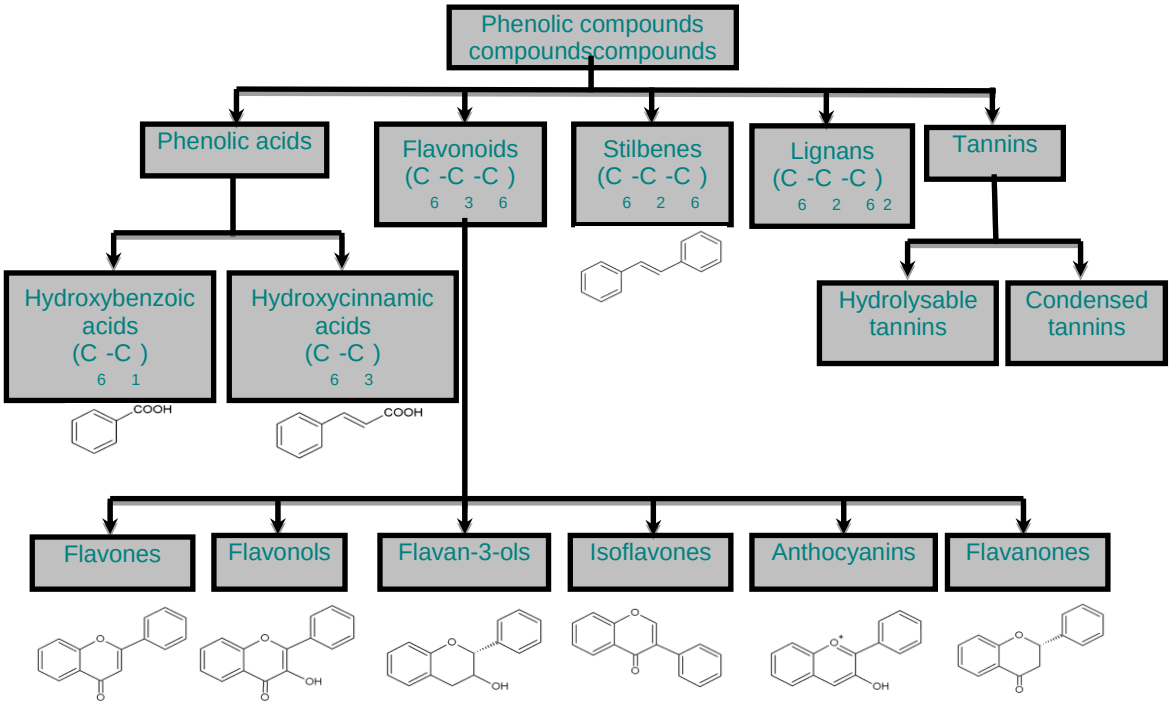

Figure 1. Classification and structure of the major phenolic compounds
(Adapted from Han *et al.*, 2007)

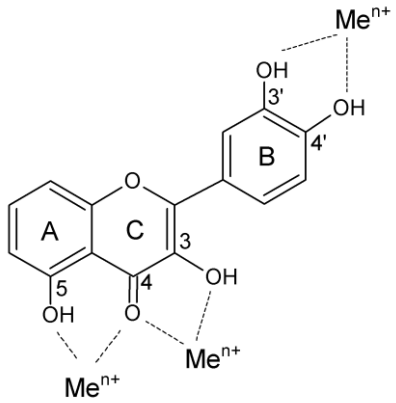

Figure 2. Complex between phenolic compounds and metals (Me^{n+})
(Leopoldini *et al.*, 2011)

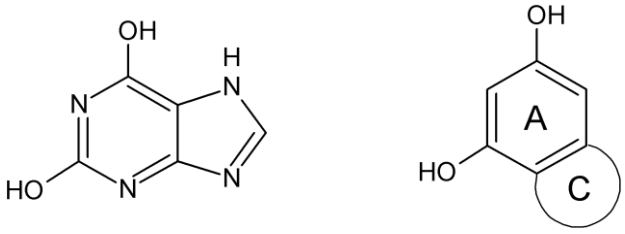

Figure 3. Similar structure between xanthine and cycle A of flavonoids

Inhibition of xanthine oxidase

The xanthine oxidase pathway is an important route in oxidative injury to tissues, especially after ischemia-reperfusion. Both xanthine dehydrogenase and xanthine oxidase are involved in the metabolism of xanthine to uric acid. Xanthine dehydrogenase is the form of the enzyme present under physiological conditions, but its configuration is changed to xanthine oxidase under ischemic conditions. Xanthine oxidase, in the reperfusion phase (*i.e.*, reoxygenation), catalyses the reaction between xanthine and molecular oxygen, releasing superoxide free radicals and uric acid (Nijveldt *et al.*, 2001).

$$\text{Xanthine} + 2O_2 + H_2O \rightarrow \text{Uric acid} + 2O_2^{\bullet -} + 2H^+$$

Flavonoids having a cycle A structure similar to the purine cycle of xanthine are considered to becompetitive inhibitors of xanthine oxidase. They may thereby inhibit the activity of xanthine oxidase as well as the formation of superoxide free radicals (Figure 3).

Relation between phenolic structure and antioxidant capacity of phenolic compounds

Phenolic structure-activity relationship studies have confirmed that the number and position of hydroxyl groups, and the related glycosylation and other substitutions largely determine the radical scavenging activity of phenolic compounds (Cai *et al.*, 2006; Leopoldini *et al.*, 2011). Phenolic compounds without any hydroxyl groups were shown to have no radical scavenging capacity. In addition, glycosylation of flavonoids diminished their activity when compared to the corresponding aglycones (Cai *et al.*, 2006). The structural requirement considered to be essential for effective radical scavenging by flavonoids is the presence of a 3',4'-dihydroxy, *i.e.* an *o*-dihydroxy group (catechol structure) in the B ring, possessing electron donating properties and serving as a radical target. Also, the 3-OH group in the C ring of flavonols is beneficial for antioxidant activity (Amic *et al.*, 2003; Lai and Vu, 2009).

This 3-OH group activity is stimulated by other donating electron groups, such as the OH groups at the 5 and 7 positions and also by the oxygen atoms at positions 1 and 4. The C_2-C_3 double bond conjugated with a 4-keto group, which is responsible for electron delocalisation from the B ring, further enhances the radical-scavenging capacity. The presence of both 3-OH and 5-OH groups in combination with a 4-carbonyl function and C_2-C_3 double bond increases the radical scavenging activity of flavonoids by being responsible for a chelating ability with transition metal ions (Amic *et al.*, 2003; Leopoldini *et al.*, 2011).

4. CARDIOPROTECTIVE ACTIVITY

Cardiovascular diseases are the leading cause of death in the United States, Europe, and Japan, and are about to become one of the most significant health problems worldwide. *In vivo* and *ex vivo* studies have provided evidence supporting the role of "oxidative stress" in leading to severe cardiovascular dysfunctions. Increased production of ROS may affect four fundamental mechanisms contributing to atherosclerosis, namely: (*i*) oxidation of low density lipoproteins (LDL) to oxidised-LDL, (*ii*) endothelial cell dysfunction, (*iii*) vascular smooth muscle cell migration and proliferation as well as matrix metalloproteinase release, and (*iv*) monocyte adhesion and migration as well as foam cell development due to the uptake of oxidised-LDL (Bahorun *et al.*, 2006). Phenolic compounds in fruits (Burton-Freeman *et al.*, 2010), cocoa powder, dark chocolate (Wan *et al.*, 2001), and coffee (Natella *et al.*, 2007) were reported to inhibit the oxidation of LDL, hence reducing cardiovascular risk. Green tea consumption reduced total and LDL cholesterol, and inhibited the susceptibility of LDL to oxidation, and was therefore associated with decreased risks of stroke and myocardial infarction (Alexopoulos *et al.*, 2010). Resveratrol and piceatannol, two stilbenes detected in red wine, were shown to elicit a number of cardioprotective activities, including inhibition of LDL oxidation, mediation of cardiac cell function, suppression of platelet aggregation, and attenuation of myocardial tissue damage during ischemic events (Roupe *et al.*, 2006). Moderate consumption of red wine rich in these stilbenes has been linked to the "French Paradox" observation described by Renaud and De Lorgeril in 1992, *i.e.* an anomaly in which southern French citizens, who smoke regularly and enjoy a high-fat diet, have a very low coronary heart mortality rate (Roupe *et al.*, 2006).

5. ANTI-INFLAMMATORY ACTIVITY

Inflammation is a dynamic process that is elicited in response to mechanical injuries, burns, microbial infection, and other noxious stimuli (Shah *et al.*, 2011). It is characterised by redness, heat, swelling, loss of function, and pain. Redness and heat result from an increase in blood flow, swelling is associated with increased vascular permeability, and pain is the consequence of activation and sensitisation of primary afferent nerve fibers. A huge number of inflammatory mediators, including kinins, platelet-activating factors, prostaglandins, leukotrienes, amines, purines, cytokines, chemokines, and adhesion molecules, have been found to act on specific targets, leading to the local release of other mediators from leucocytes and the further attraction of leucocytes, such as neutrophils, to the site of inflammation. Under normal conditions, these changes in inflamed tissues serve to isolate the effects of the insult and thereby limit the threat to the organism. However, low-grade chronic inflammation is considered a critical factor in many diseases including cancers, obesity, type II diabetes, cardiovascular diseases, neurodegenerative diseases, and premature aging (Santangelo *et al.*, 2007).

Phenolic compounds have been reported to display marked *in vitro* and *in vivo* anti-inflammatory properties via various mechanisms of action including: (*i*) inhibition of

the arachidonic acid pathway, (*ii*) modulation of the nitric oxide synthetase family, and (*iii*) modulation of the cytokine system as well as of the nuclear factor kappa B (NF-kB) and mitogen-activated protein kinase (MAPK) pathways (Figure 4) (Santangelo *et al.*, 2007).

5.1. Inhibition of the arachidonic acid pathway

Arachidonic acid plays a key role in inflammation. Arachidonic acid is released from phosphoglyceride membranes by the catalytic action of phospholipase A_2 and is further metabolised through the cyclooxygenase (COX) pathway into prostaglandins and thromboxanes A_2 or by the lipoxygenase pathway to leukotrienes (Santangelo *et al.*, 2007), all being mediators of inflammation. Flavonoids, including quercetin, kaempferol, galangin, and their derivatives, showed good inhibitory activity on phospholipase A_2 (Lättig *et al.*, 2007). Phenolic compounds extracted from berry fruits inhibited the activity of both COX1 and COX2(Bowen-Forbes *et al.*, 2010). Lipoxygenase was also inhibited by a phenolic extract from *Ziziphus mistol* ripe berries (Cardozo *et al.*, 2011). The inhibition of these enzymes leads to a decrease of eicosanoid levels in the inflammatory process (Figure 4).

5.2. Modulation of the nitric oxide synthetase family

Nitric oxide (NO) is an important cellular mediator involved in numerous physiological and pathological processes of inflammation. NO is synthesised from L-arginine by the members of the nitric oxide synthetase (NOS) family,

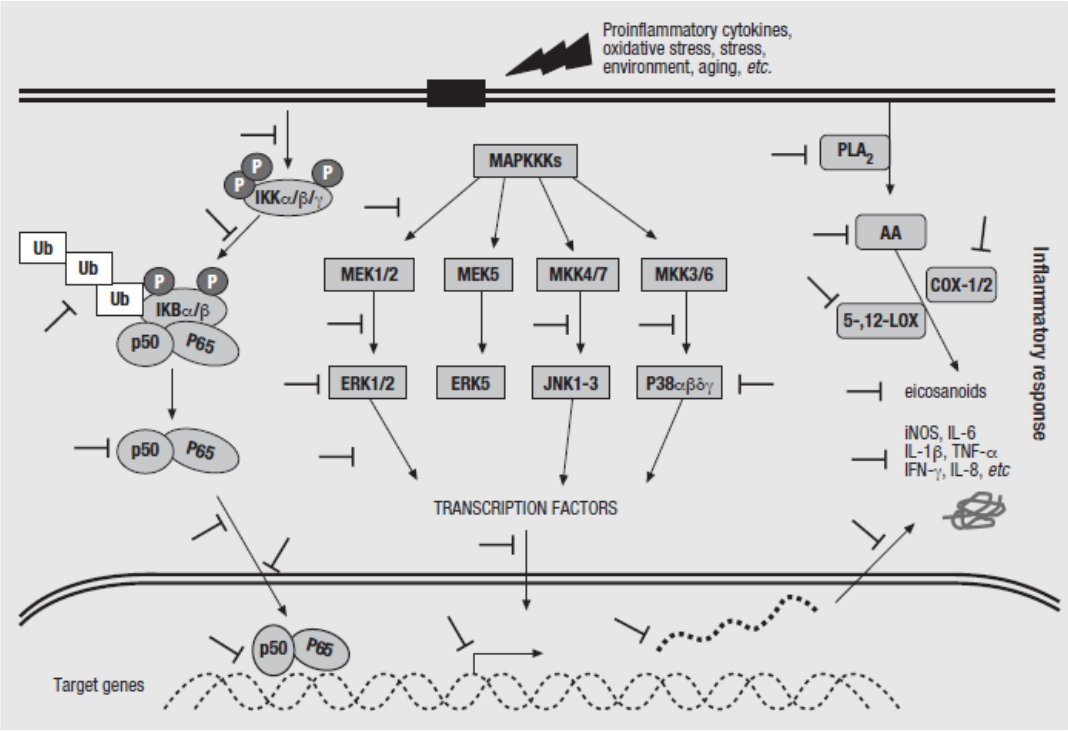

Figure 4. Potential points of action of phenolic compounds (⊥) within the inflammatory cascade (Santangelo *et al.*, 2007)

Note: IKB, inhibitor kB; Ub, ubiquitin; IKK, IkB-kinase; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8; IFNγ, interferon-γ; AA, arachidonic acid; LOX, lipoxygenase; COX, cyclooxygenase; PLA2, phospholipase A_2; ERK, extracellular signal-related kinase; JNK, c-Jun amino-terminal kinase; MEK (or MKK), MAPK-kinase; MAPKKK, MAPK kinase kinase; TNF-α, tumour necrosis factor-α; iNOS, inducible nitric oxide synthase; p38 (or p38-MAPK), p38-mitogen-activated protein kinase.

which includes endothelial (eNOS), neuronal (nNOS), and inducible (iNOS) isoforms. While a small amount of NO, synthesised by eNOS and nNOS, is essential to maintain normal body functions (homeostasis), a significant increase of NO synthesised by iNOS participates in the inflammatory processes and acts synergistically with other inflammatory mediators (Santangelo *et al.*, 2007). Phenolic compounds extracted from the roots of Ulmus macrocarpa (Kwon *et al.*, 2011) and citrus fruit peels (Choi *et al.*, 2007), showed an inhibitory action on NO production. In mice, where liver inflammation was induced by intravenous injection of heat-killed Propionibacterium acnes and lipopolysaccharide, the concentration of NO in the liver was markedly increased. However, a significant concentration-dependent inhibition of NO production was detected when mice were orally administrated a phenolic extract from tea flowers (Camellia sinensis) (Chen *et al.*, 2012). The inhibition of NO formation was caused by the suppression of iNOS gene expression by, for example, chlorogenic acid and anthocyanins of blueberry (Lau *et al.*, 2009); kaempferol (Kim *et al.*, 2015); catechin 7-O-β-D-apiofuranoside, (+)-catechin, and taxifolin 6-C-glucopyranoside from the roots of Ulmus macrocarpa (Kwons *et al.*, 2011); and also suppression of iNOS activity by chlorogenic acid and anthocyanins of blueberry (Lau *et al.*, 2009) (Figure 4).

5.3. Modulation of the cytokine system as well as of the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways

NF-κB transcription factors have been suspected to play a key role in chronic and acute inflammatory diseases. In unstimulated cells, the NF-κB factors are sequestered in the cytoplasm in an inactive non-DNA-binding form, associated with inhibitor κB proteins (IκBs). Upon cell stimulation, IκB proteins are rapidly phosphorylated by IκB kinase and dissociated from NF-κB. The released NF-κB can then translocate into the nucleus and induce the expression of various genes encoding pro-inflammatory cytokines (e.g., IL-1, IL-2, IL-6, and TNF-α), chemokines (e.g., IL-8 and MCP-1), and inducible enzymes such as COX2 and iNOS (Santangelo *et al.*, 2007). Phenolic compounds were shown to have an anti-inflammatory activity by modulating NF-κB activation in multiple steps of the process (Figure 4). 100 μmol of kaempferol blocked the activation of tyrosine kinases (Syk and Src kinases) and inhibited the activation of NF-κB factors in lipopolysaccharide (LPS)-activated RAW264.7 cells, a murine macrophage cell line used as an in vitro model (Kim *et al.*, 2015). Electrophilic quinone formed from piceatannol oxidation was suggested to directly interact with critical cysteine thiols of IκB kinase, hence inhibiting the activation of NF-κB in MCF-10A cells (Son *et al.*, 2010). By another way, ethyl caffeate extracted from a medical plant named Bidens pilosa suppressed activation of NF-kB through the inhibition of the NF-κB-DNA complex formation in vitro and in vivo (in mouse skin) (Chiang *et al.*, 2005). The decrease of expression at the transcriptional level of TNF-α and IL-1β in induced mice by tea flower extract (Chen *et al.*, 2012) could also be caused by the suppressed activation of NF-κB factors.

MAPKs are a family of Ser/Thr kinases that regulate important cellular processes, including cell growth, proliferation, death, and differentiation, by modulating gene transcription in response to changes in the cellular environment. They constitute upstream regulators of transcription factor activities. Among the MAPK family members, mitogen and growth factors frequently activate the extracellular signal-regulated kinase (ERK) route, while stress and inflammation constitute the main triggers for the c-Jun N-terminal kinase (JNK) and the p38 cascade (Santangelo *et al.*, 2007). Kaempferol suppressed the phosphorylation of MKK3 and MKK4 kinases in LPS-induced RAW264.7 cells and inhibited the activation of activator protein 1 (AP-1). This inhibition could contribute to the decrease in prostaglandin E2 production (Kim *et al.*, 2015).

6. ANTI-CANCER ACTIVITY

Cancer is characterised by two biological properties, the uncontrolled growth of cells in the human body (endless proliferation) and the ability of these cells to migrate from the original site to distant sites (invasion). It is caused by exposure to a variety of carcinogens, including tobacco smoke, alcoholic drinks, industrial carcinogens, aflatoxins, heterocyclic amines, N-nitroso compounds, and polycyclic aromatic hydrocarbons. A wide variety of natural bioactive compounds, including polyphenols, have been shown to inhibit carcinogenesis (Demeule *et al.*, 2002).

Phenolic compounds act as anti-cancer agents by various mechanisms of action including: (i) their antioxidant properties (Demeule *et al.*, 2002), (ii) the modulation of signal transduction pathways (Roupe *et al.*, 2006), (iii) the induction of apoptosis, (iv) the arrest of the cell cycle (Wang *et al.*, 2011), and (v) the inhibition of cancer cell invasion (Kita *et al.*, 2012).

The first anti-cancer effect of phenolic compounds is due to their antioxidant activity. In the case of oxidative stress, excessive ROS/RNS induce DNA damage, alter gene expression, or affect cell growth and differentiation, leading to the appearance of cancer (Demeule *et al.*, 2002). Phenolic compounds with their antioxidant capacities inhibit the harmful effects of ROS/RNS and prevent cancer.

The second anti-cancer mechanism of phenolic compounds concerns their effect on the signal transduction pathways, including inhibition of receptor tyrosine kinases and of MAPKs.

Growth factors are usually proteins or steroid hormones that bind to specific receptors on the cell surface to elicit a signalling cascade responsible for the normal activation of cell proliferation/differentiation required for tissue growth and repair. Among them, epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), transforming growth factors-α and -β (TGFs-α and -β), insulin-like growth factor (IGF), and erythropoietin (EPO) are the major growth factors implicated in carcinogenesis (Wahle *et al.*, 2009). These factors can selectively interact with the phosphorylated activated receptors and activate downstream signalling pathways that ultimately lead to gene transcription and to cell proliferation. Under physiological conditions, the receptor tyrosine kinases are at equilibrium between the inactive - unphosphorylated and the active - phosphorylated states. Enhanced activity of receptor tyrosine kinases is implicated as a contributing factor in the development of malignant proliferation of diseases such as cancer (Demeule *et al.*, 2002). Delphinidin has been reported to inhibit a broad spectrum of receptor tyrosine kinases of the epidermal growth factor receptor ErbB and vascular endothelial growth factor receptor (VEGFR) families in cell-free and cell test systems (Teller *et al.*, 2009). (-)-Epigallocatechin gallate, a major antioxidant constituent of green tea, inhibited tyrosine phosphorylation of the platelet-derived growth factor β-receptor and then the downstream activation of the extracellular signal-regulated kinase and phosphatidyl inositol 3-kinase/Akt pathways, which have been shown to contribute to the proliferation and migration of rat pancreatic stellate cells (Masamune *et al.*, 2005). Epigallocatechin gallate markedly inhibited the phosphorylation of the EGF HER-2/neu receptor (HER-2) whose overexpression was associated with a poor prognosis in patients with breast carcinoma (Masuda *et al.*, 2003).

MAPKs participate in the activation of activator protein 1 (AP-1), a transcription factor, and influence the expression of many genes involved in cell growth, proliferation, death, and differentiation (Santangelo *et al.*, 2007). Elevated MAPK and AP-1 activities are involved in many disease-related processes such

as neoplastic transformation, cancer cell invasion, metastasis, and angiogenesis (Demeule *et al.*, 2002). Phenolic compounds have been shown to inhibit the activation of AP-1 through inhibition of the ERK pathway. Indeed, a blackberry extract blocked UVB- and TPA-induced phosphorylation of ERKs and JNKs, hence decreasing the 12-O-tetradecanoylphorbol-13-acetate induced neoplastic transformation of JB6 P+ cells (Feng *et al.*, 2004). Chlorogenic acid decreased the phosphorylation of JNKs, p38 kinase, and MAP kinase 4, hence suppressing the TPA-induced neoplastic transformation of JB6 P^+ cells (Feng *et al.*, 2005).

The third mechanism of phenolic's anticancer activity is the induction of apoptosis. Phenolic compounds have been shown to inhibit growth and induce apoptosis in a variety of mammalian cell lines. Indeed, phenolic compounds from three blueberry cultivars were reported to induce the apoptosis of two colon cancer cell lines, HT-29 and Caco-2. Among them, the anthocyanin fraction had the highest efficiency (IC50 = 15-50 μg/mL), followed by the flavonol (IC50 = 70-100 μg/mL) and tannin (IC50 = 50-100 μg/mL) fractions, while the phenolic acid fraction had the smallest (IC50 about 1000 μg/mL) (Yi *et al.*, 2005). Extracts rich in anthocyanins from plums and peaches exhibited growth inhibitory effects on human colon cancer cells, including Caco-2, SW1116, HT29, and NCM460 cells (Lea *et al.*, 2008). A phenolic extract of *Solanum nigrum* L., a herbal plant indigenous to South-East Asia and commonly used in oriental medicine, was reported to reduce the viability of hepatocellular carcinoma cells ($HepG_2$) by arresting the G_2/M phase of the cell cycle (4^{th} mechanism of action) and inducing apoptosis (Wang *et al.*, 2011). Piceatannol was reported to suppress both the proliferation, by way of inducing apoptosis, and the invasion (5^{th} mechanism of action) of AH109A hepatoma cells *in vitro* and *ex vivo* by Kita *et al.* (2012).

7. ANTIMICROBIAL ACTIVITY

Phenolic compounds have been found *in vitro* to be effective antimicrobial substances against a wide array of microorganisms, including bacteria (Taguri *et al.*, 2006; Okoro *et al.*, 2010; Dang *et al.*, 2015), yeasts (Okoro *et al.*, 2010; Huwaitat *et al.*, 2013), and fungi (Hussin *et al.*, 2009), involved in human diseases and deterioration of foods. Inhibitive mechanisms of phenolic compounds on microbial growth include: (*i*) substrate depletion (*e.g.*, iron and tyrosine) (Cowan *et al.*, 1999; Okoro *et al.*, 2010), (*ii*) complex formation with surface-exposed proteins and with membrane-bound enzymes leading to the dysfunction of the cytoplasmic membrane and cell wall (Cowan *et al.*, 1999; Huwaitat *et al.*, 2013), (*iii*) interaction with eukaryotic DNA and inhibition of growth (Kuete *et al.*, 2007), and (*iv*) inhibition of enzyme actions through non-specific interactions with proteins and inhibition of various types of oxidizing enzymes through reactions with sulfhydryl groups (Okoro *et al.*, 2010). In addition, some lipophilic phenolic compounds may penetrate and disrupt the microbial membrane (Cowan *et al.*, 1999).

Antimicrobial properties of phenolic compounds depend on their hydroxylphenyl structure (Taguri *et al.*, 2006; Nitiema *et al.*, 2012). By testing the antimicrobial activity of 22 phenolic compounds on 26 species of bacteria, Taguri *et al.* (2006) found that phenolic compounds that had pyrogallol groups had a strong antibacterial activity, while those with catechol and resorcinol rings showed a lower activity. Indeed, a large number of hydroxyl groups enables phenolic compounds to form complexes with proteins and then inhibit microbial growth. However, coumarin containing any hydroxyl group exhibited a greater antibacterial activity against some *Escherichia coli* and *Salmonella infantis* species than quercetin, a flavonoid having five hydroxyl groups. The higher lipophilic property of coumarin might help it to penetrate the

cytoplasmic membrane of bacteria and disrupt it (Nitiema *et al.*, 2012).

8. CONCLUSIONS

Phenolic compounds represent a large group of secondary metabolites produced in plants. Epidemiological studies strongly support a role for polyphenols in the prevention of cardiovascular diseases, cancers, osteoporosis, diabetes mellitus, arthritis, and neurodegenerative diseases, which are associated with "oxidative stress" and chronic inflammation. The mechanisms of biological actions were also analysed, and little by little understood. However, in order to have deep knowledge about the effects of phenolic compounds on human health, further research needs to be done, such as the compounds' accessibility and bioavailability in the human body.

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