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Review

Flavonoids and phenolic acids: Role and biochemical activity in plants and human

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Flavonoids and phenolic acids make up one of the most pervasive groups of plant phenolics. Due to their importance in plants and human health, it would be useful to have a better understanding of flavonoid concentration and biological activities that could indicate their potentials as therapeutic agents, and also for predicting and controlling the quality of medicinal herbs. Plants and herbs consumed by humans may contain thousands of different phenolic acid and flavonoid components. The effect of dietary phenolics is currently of great interest due to their antioxidative and possible anticarcinogenic activities. Phenolic acids and flavonoids also function as reducing agents, free radical scavengers, and quenchers of singlet oxygen formation. In addition, flavonoids and phenolic acids components play important roles in the control of cancer and other human diseases.

Key words: Flavonoids, phenolic acids, biological activities, antioxidative, anticarcinogenic.

INTRODUCTION

Natural bioactive compounds especially from plant sources, including spices have been investigated for their characteristics and health effects. Plants are potential sources of natural bioactive compounds such as secondary metabolites and antioxidants. They absorb the sun light and produce high levels of oxygen and secondary metabolites by photosynthesis. Medicinal components produced are stored in plant leaves. Most of the secondary metabolites of herbs and spices are commercially important and find use in a number of pharmaceutical compounds. Flavonoids and phenolics acids are the most important groups of secondary metabolites and bioactive compounds in plants (Kim et al., 2003). They are also a kind of natural product and antioxidant substance capable of scavenging free superoxide radicals, anti-aging and reducing the risk of cancer. Secondary metabolites are chemicals produced by plants; and their functions in growth, photosynthesis, reproduction and other primary processes are not known yet. Secondary chemicals are important in plant use by widely used especially in Asia (Bodeker, 2000). It was found that flavonoids reduce blood-lipid and glucose of humans. Most pharmaceuticals are based on plant component structures; as such, secondary metabolites enhance human immunity (Atoui et al., 2005). Flavonoids constitute a wide range of substances that play important role in protecting biological systems against the harmful effects of oxidative processes on macromolecules, such as carbohydrates, proteins, lipids and DNA (Halliwell and Gutteridge, 1989). Vaquero et al. (2007) investigated the properties of quercetin, rutin, caffeic acid, vanillic acid and gallic acid of different wine against pathogenic microorganisms. In addition, Demetzos et al. (2001) reported the antimicrobial activity of myricetin that could inhibit Gram-positive bacteria compared to Gram-negative. Furthermore, Li and Xu (2008) and Mandalari et al. (2007) mentioned antimicrobial activity of naringin and quercetin. Flavonoids are able to inhibit aldose reductase enzyme (that converts sugars to sugar alcohols) and is implicated with diabetic complications, such as neuropathy, heart disease and retinopathy (Thorne Research, Inc., 2001).

Antidiabetic activity of flavonoids and phenolic acids has been reported by several studies (Weiss et al., 2011; Lu et al., 2011). Phenolic compounds are famous group of secondary metabolites with wide pharmacological activities. Varied biological activities of phenolic acids were reported. Increases bile secretion, reduces blood

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cholesterol and lipid levels and antimicrobial activity against some strains of bacteria such as staphylococcus aureus are some of biological activities of phenolic acids (Leung, 1980). Phenolics and flavonoids possess diverse biological activities, for instance, antiulcer (Matsuda et al., 2003), anti-inflammatory (Araujo and Leon, 2001), antioxidant (Ghasemzadeh et al., 2011), cytotoxic and antitumor (Murakami et al., 2004), antispasmodic (Ammon and Wahl, 1991), and antidepressant activities (Yu et al., 2002). Dietary polyphenolic compounds, with emphasis on quercetin (found in appreciable levels in Vaccinium), were shown to inhibit collagenstimulated platelet activation through multiple components of the glycoprotein VI signaling pathway (Hubbard et al., 2003).

PHENOLIC ACIDS

Phenolic acids are secondary metabolites extensively spread throughout the plant kingdom. Phenolic compounds confer unique taste, flavour, and health-promoting properties found in vegetables and fruits (Tomas-Barberan and Espin, 2001). Therefore, increasing the phenolic content in these plants can enhance their quality. Phenolic compounds are crucial for plants growth and reproduction, and are produced as a response to environmental factors (light, chilling, pollution etc) and to defend injured plants (Valentine et al., 2003). Minimal attention has been directed toward examining the possible effects of mild environmental stresses on their phytochemical composition. Nevertheless, there are numerous studies showing the effect of environmental stresses on antioxidant accumulation in relation to plant adaptation. Pennycooke et al. (2005) reported that chilling stress is led to elevated total phenolic content and antioxidant capacity in petunia. Similarly, high irradiation and cold stress can lead to elevated levels of flavonoids in plants (Kreps et al., 2002; Tattini et al., 2005). In recent years, the importance of antioxidant activities of phenolic compounds and their potential usage in processed foods as a natural antioxidant compounds has reached a new level. Results of previous studies provided phenolic acid compounds are to be universally distributed in plants (Elzaawely et al., 2007; Dai and Mumper, 2010).

Phenolic acid compounds and functions have been the subject of a great number of agricultural, biological, chemical and medical studies. These compounds form a diverse group that includes the widely distributed hydroxybenzoic and hydroxycinnamic acids. Hydroxycinnamic acid compounds are (often) produced as simple esters with glucose or hydroxy carboxylic acids. Plant phenolic compounds are diverse in molecular structure, and are characterized by hydroxylated aromatic rings (Mandal et al., 2010). The phenolic compounds are categorized as secondary metabolites, and their function in plants is poorly understood. Phenolic compounds in many plants are polymerized into larger molecules such as the proanthocyanidins (PA; condensed tannins) and lignins. Moreover, phenolic acids may arise in food plants as glycosides or esters with other natural compounds such as sterols, alcohols, glucosides and hydroxyfatty acids.

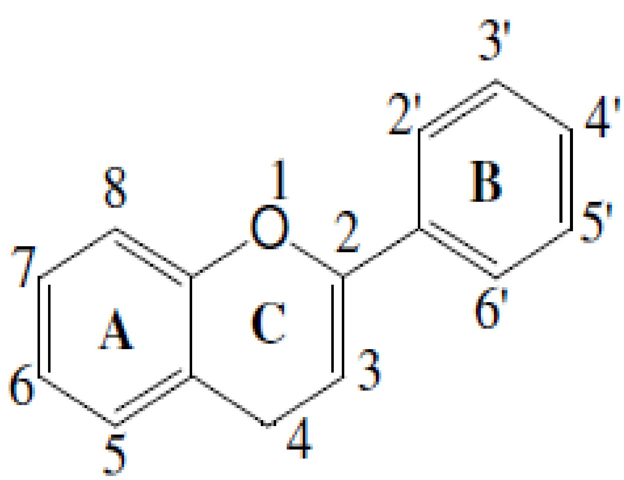

Figure 1. Phenol structure.

FLAVONOIDS

Like as phenolic acids, flavonoids are secondary metabolites of plants with polyphenolic structure. They are synthesized by the polypropanoid pathway and the start up component is phenylalanine molecule. The biological effects of these compounds vary. All flavonoids share the basic C_6-C_3-C_6 structural skeleton, consisting of two aromatic C6 rings (A and B) and a heterocyclic ring (C) that contains one oxygen atom (Figure 1). They have been classified into six subgroups (Figure 2):

1. Flavones (luteonin, apigenin, tangeritin).
2. Flavonols (quercetin, kaemferol, myricetin, isorhamnetin, pachypodol).
3. Flavanones (hesteretin, naringenin, eriodictyol).
4. Flavan-3-ols: catechins and epicatechins.
5. Isoflavones (genistein, daidzein, glycitein).
6. Anthocyanidins compounds (cyanidin, delphinidin, malvidin, pelargonidin, peonidin, petunidin).

Other common flavonoid groups include aurones, xanthones, and condensed tannins. The catechins and leucoanthocyanidins are structurally similar and only rarely exist as their glycosides. Most of flavonoids are present in our daily life (Manach et al., 2004; Dahan and Altman, 2004). To date, about 6000 flavonoid compounds have been isolated and identified, and many are common in higher plants (Tolonen et al., 2002; Austin and Noel, 2003). Most flavonoid compounds which are often accumulated in the vacuoles of plant cells are glycosides.

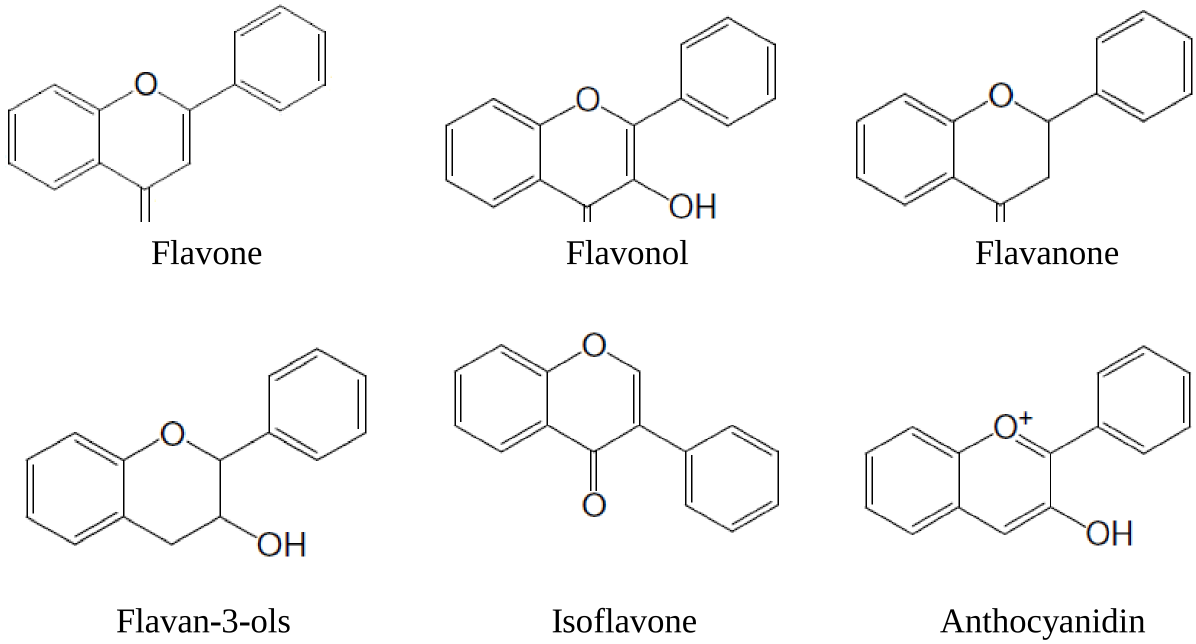

Figure 2. Structure of some phenolic acids.

Glycosides can either be O- or C- linked. The variant of flavonoid glycosides are based on the number of positions on the flavonoid for glycosylation, the level of glycosylation and the number of types of sugars involved in glycosylation. Furthermore, of the several hundred aglycones isolated from plants, only eight are distributed widely (Seigler, 1998) and the eight most common flavonoid nuclei are kaempferol, quercetin, rutin, catechin, epicatechin, myricetin, anthocyanidins and luteolin.

MEDICINAL PROPERTIES OF PHENOLICS AND FLAVONOIDS

Antioxidant properties of phenolics and flavonoids

Oxidative stress is considered to be substantial, if not crucial, in the initiation and development of many current conditions and diseases, including: inflammation, autoimmune diseases, cataract, cancer, parkinson's disease, arteriosclerosis and aging (Lukyanova et al., 2007). Oxidative stress plays a role in heart diseases, neurodegenerative diseases, cancer and in the aging process (Zima et al., 2001; Astley, 2003). This theory is supported by increasing evidence suggesting/indicating that oxidative damage plays a role in the development of chronic, age-related degenerative diseases, and that dietary antioxidants oppose this and lower the risk of disease (Atoui et al., 2005). Antioxidants are substances that significantly delay or prevent the oxidation of an oxidisable substrate when present in low concentrations compared to the substrate (Lucio et al., 2009).

Flavonoids are well known for their antioxidant activity. Antioxidants are specific compounds that protect human, animal and plant cells against the damaging effects of free radicals (reactive oxygen species, ROS). An imbalance between antioxidants and free radicals results in oxidative stress, will/may lead to cellular damage (Kukic et al., 2006). At present, most antioxidants are manufactured synthetically, belonging to the class of synthetic antioxidants. The main disadvantage of synthetic antioxidants is the side effects when consumed *in vivo* (Chen et al., 1992). Plants are potential sources of invaluable antioxidants. Natural or phytochemical antioxidants are secondary metabolites in plants (Dai and Mumper, 2010) such as phenolic acids, flavonoids and carotenoids, which are amongst the antioxidants produced by plants for their sustenance (Apak et al., 2007). Recently, phenolics and flavonoids have been considered as great antioxidants and proved to be more effective than Vitamin C, E and carotenoids (Dai and Mumper, 2010). The antioxidant properties of phenolic and flavonoid compounds are mediated by the following mechanisms: (1) scavenging radical species such as ROS/ reactive nitrogen species (RNS); (2) suppressing ROS/RNS formation by inhibiting some enzymes or chelating trace metals involved in free radical production; (3) up regulating or protecting antioxidant defense (Cotelle, 2001). The reduction activity of phenolic and flavonoid compounds depends on the number of free hydroxyl groups in the molecular structure, which would be strengthened by steric hindrance (Rice-Evans et al., 1996).

Luteolin is a flavone that acts as antioxidant, free radical scavenger, anti-inflammatory agent, immune system modulator and cancer prevention agent (Seelinger et al., 2008). Flavonoids from tea, cocoa, chocolate, fruits, vegetables and wine, are highly potent antioxidant compounds that help to reduce incidence of stroke, heart failure, diabetes and cancer. Their anticancer effects have been thoroughly investigated. Apart from antioxidant positive effects on improving health, antioxidants are also added in food to prevent or delay the oxidation of food, initiated by free radicals formed during their exposure to environmental factors such as air, light and temperature (Hras et al., 2000). Ghasemzadeh and Jaafar (2011) reported that the isolated polyphenols from young ginger (*Zingiber officinale*) including quercetin, kaempferol, rutin gallic acid, were shown to inhibit the growth of human breast cancer cell lines (MCF–7 and MDA–MB–231).

Anticancer properties of phenolics and flavonoids

Cancer is a multi-step disease incorporating physical, environmental, metabolic, chemical and genetic factors, in which each plays a direct and/or indirect role in the induction and deterioration of cancers. Diet with high consumption of antioxidant rich fruits and vegetables reduces the risk of many cancers types, significantly suggesting that these antioxidants could be effective agents to inhibit cancer (Fimognari et al., 2005). Antioxidants in the diet are very promising as cancer inhibitors because of their low toxicity, safety and general acceptance (Ogasawara et al., 2007; Ramos, 2007). Isolated polyphenols from different plants have been considered in a number of cancer cell lines at different stages of cancer growth. For example, the isolated polyphenols from strawberry including kaempferol, quercetin, anthocyanins, coumaric acid and ellagic acid, were shown to inhibit the growth of human breast (MCF-7), oral (KB, CAL-27), colon (HT-29, HCT-116), and prostate (LNCaP, DU-145) tumor cell lines (Zhang et al., 2008; Damianaki et al., 2000). Similar results have also been reported in previous studies with wine extracts and isolated polyphenols (resveratrol, quercetin, catechin and epicatechin) as well as green tea polyphenols (epigallocatechin, epicatechin) (Weisburg et al., 2004). Additionally, Manthey et al. (2001) reported that citrus flavonoids inhibited the growth of HL-60 leukemia cells.

Kaempferol, which is also a type of flavonoid, was shown to inhibit the growth of ovarian cancer cell lines (91%), and A2780/CP70 (94%) by concentration of 20 and 40 μM, respectively as well as breast cancer cell lines (Luo et al., 2009). Epigallocatechin 3-gallate is an effective antiangiogenesis agent which inhibits tumor cell invasion and proliferation (Tang et al., 2007) and, inhibits growth of the NBT-II bladder tumor cells and breast cancer cell lines (Chen, 2004). Several studies revealed that quercetin's significant anti-inflammatory activity is due to the direct inhibition of initial processes in inflammation (Park et al., 2008). Additionally, potent anticancer activity of quercetin has been demonstrated as well. For example, some tests showed its antitumor properties including the inhibition of cancer cells proliferation and migration (Lim et al., 2006). Combined application of quercetin and ultrasound on skin and prostate cancer showed 90% mortality within 48 h with no visible mortality on normal cells (Paliwal et al., 2005). Significantly higher anticancer activities of gallic acid, caffeic acid and ferulic acid have been reported earlier (Hwang et al*.,* 2006; Madlener et al., 2007).

The function of flavonoids in plants

Flavonoids have various roles in plants, but they are not understood completely yet.

Plant-microorganism communication

Flavonoid compounds have roles as signal molecules, phytoalexins, detoxifying agents and stimulants for germination of spores.

Stimulant or protection

Flavonoids may have a stimulant or protective role depending on the roles of the microorganisms in the plant.

Pigments

The colours of flowers, fruits, and leaves of plants are related to anthocyanins.

Flavouring

Flavonoids are amongst of the chemicals that give the plant a rich taste (Harbone, 1976). The flavour may act as an attractant or repellent to pollinators or pests.

Phenolics and flavonoids biosynthesis in plants

The shikimic acid pathway (Figure 3) is a major route for biosynthesis of aromatic compounds in plants and microorganisms including the proteinaceous amino acids phenylalanine, tyrosine and tryptophan. Flavonoids are synthesized via the phenylpropanoid pathway (Figure 1). Phenylalanine, tyrosine and tryptophan are the primary metabolites which serve as precursors for many natural (secondary) products such as flavonoids, phenolic acids, coumarins, alkaloids, glucosinolates and cyanogenic glycosides (Wink, 2010). In addition to these secondary

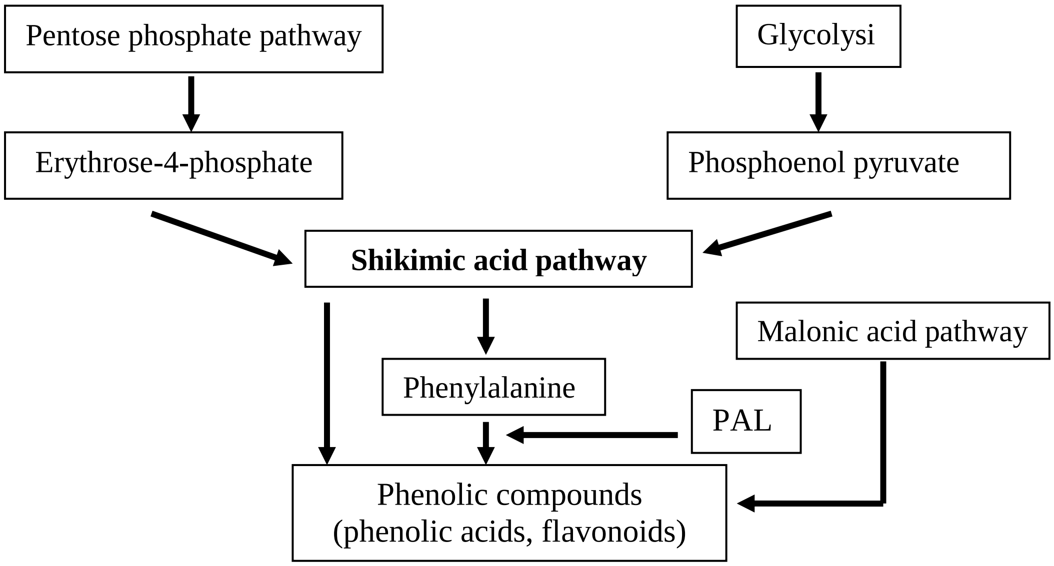

Figure 3. The flavonoid biosynthetic pathway. Enzyme abbreviations: PAL, phenylalanine ammonia-lyase; C4H, cinnamate 4-hydroxylase; 4CL, 4-coumaroyl:CoA ligase; CHS, chalcone synthase; CHI, chalcone isomerase; F3´H, flavanone 3-hydroxylase; F3´H, flavonoid 3´ hydroxylase; F3´5´H, flavonoid 3´5´ hydroxylase; FLS, flavonol synthase; DFR, dihydroflavonol 4-reductase; LCR, leucoanthocyanidin reductase; ANR, anthocyanidin reductase; ANS, anthocyanidin synthase; UFGT UDP glucose-flavonoid 3-O-glucosyl transferase; RT, rhamnosyl transferase; MT, methyltransferase.

compounds, the shikimic acid pathway provides precursors for many ubiquitous compounds important in a plant's life such as the structural element lignin, the growth hormone indole acetic acid, quinones of the electron transport chain and storage compounds like caffeoyl-quinate (Conn, 1986). Most secondary metabolites with antioxidant properties including the diverse group of phenolic compounds are synthesized through the shikimic acid pathway. Although malonic acid pathway is also involved in the biosynthesis of some of these compounds (flavonoids); its role is rather minor in higher plants (Taiz and Zeiger, 1998). The first key step in the shikimic acid pathway is the condensation of erythrose-4-phosphate from the pentose phosphate pathway (Herrmann and Weaver, 1999). Shikimic acid pathway leads to the formation of three aromatic amino acids; tryptophan, tyrosine and phenylalanine. Most phenolic compounds classes are derived from phenylalanine although hydrolyzable tannin is directly produced through the gallic acid in the shikimic acid pathway. The production of phenolic compounds is catalyzed by phenylalanine ammonia-lyase (PAL), whereby. PAL is a key gateway enzyme in the secondary metabolic pathway leading to the synthesis of phenolic compounds. The control of PAL activity seems to be a key factor in regulating this pathway (Jones, 1984). To evaluate its roles in plants, several studies were conducted using 2-aminoindan-2-phosphonic acid (AIP), which is a key inhibitor of PAL activity and is considered as a stronger inhibitor than 2-aminooxyacetate (AOA) and 2-aminooxy-3-phenylpropanoic acid (AOPP) (Appert and Amrhein, 2003). In one study, it was found that inhibition of inhibits PAL activity by AIP, prevented browning in cut lettuce caused by the accumulation of phenolic compounds during cold storage (Hisaninato et al., 2001). In another study, Keski-Saari (2005) found that inhibition of PAL by AIP treatment significantly decreased the content of total phenolic compounds. Thus, these results suggested that in addition to being the rate-limiting enzyme for secondary metabolites, PAL also plays an important role in plant stress tolerance. Ghasemzadeh et al. (2010) showed that synthesis of phenolics and flavonoids in ginger can be increased and affected by using CO_2 enrichment in a controlled environment and following that, the antioxidant activity in young ginger extracts could also be improved.

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