

## Phenolic compounds: structures and activities

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### RESEARCH ARTICLE

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**Abstract:** Phenolic compounds are secondary metabolites found in most plant tissues, including fruits and vegetables. They are produced via shikimic acid and phenylpropanoid pathways. The most common classification implies the subdivision of phenolic in two main groups: flavonoids (e.g., anthocyanins, flavanols, flavanones, flavonols, flavonones, and isoflanones) and non-flavonoids (e.g., phenolic acids, coumarins, stilbenes, lignans, lignins and tannins) polyphenols. Such variations give them a wide range of biological and potential therapeutic activities such as antioxidant, anti-inflammatory and anticancer, among others. Their

structures and functions are much discussed by previous researchers. This review provides a comprehensive overview of phenolic compound structures and properties.

**Keywords:** phenolic compounds, structures, activities.

### Introduction

Plant metabolism is mainly classified as primary or secondary. Compounds produced through primary metabolism, which are generally referred to as primary metabolites; include sugars, fatty acids, amino acids, and nucleic acids ( Kasote et al., 2015). Secondary metabolites are classified as aliphatic compounds (terpenes and terpenoids, resin acids, sterols, fats, waxes, fatty acids), phenolic compounds (flavonoids, simple phenols, tannins, stilbenes), and other secondary metabolites ( sugar, alkaloids) (Metsämuuronen and Sirén, 2019). Primary metabolites are required for the maintenance of plant cells, while secondary metabolites are essential to the normal growth, development, and defense of plants ( Kasote et al., 2015). The three major secondary metabolites of plants are phenolics, terpenoids, and nitrogenous organic compounds ( Yang et al., 2020). Phenolic compounds are the most widely distributed secondary metabolites, ubiquitously present in the plant kingdom, with immense structures and functions. They are considered one of the abundant classes of phytochemicals with health-promoting qualities and functions ( Swallah et al., 2020). Phenolic compounds, or polyphenols, constitute one of the most numerous and widely distributed groups of substances in the plant kingdom, with more than 8.000 phenolic structures currently known ( Urquiaga and Leighton, 2000). They are important secondary metabolites in fruits, vegetables, tea, coffee, chocolates, legumes, cereals, and beverages ( Ganesan and Xu, 2017). They are present in all organs of the most diverse plants ( fruits, seeds, roots, bark, wood, and leaves) (Teplova et al., 2018). They have a common element, which is the presence of at least one hydroxyl group on an aromatic ring. It can contain

a free hydroxyl or another functional group (ether, ester, or heteroside) (Garcia-Pérez et al., 2017; Elazzouzi et al., 2019).

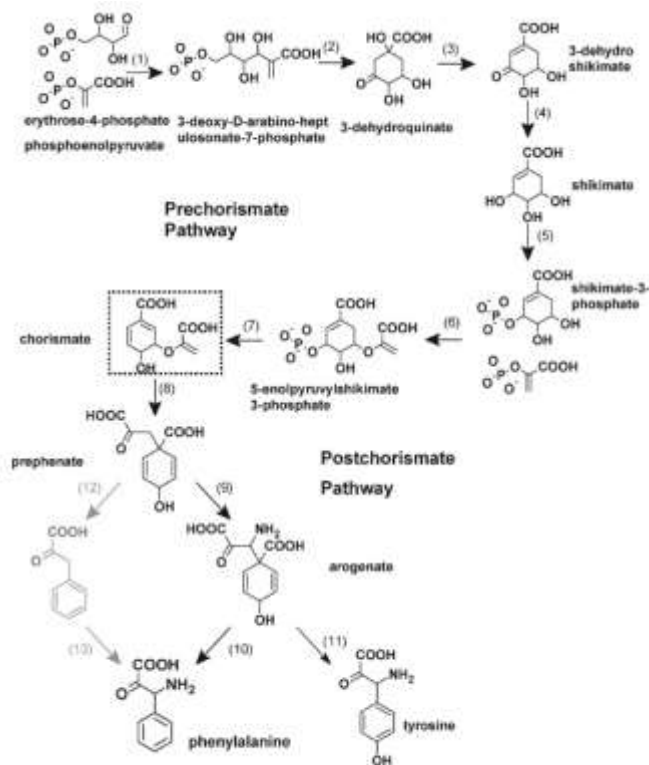
### Roles and activities of polyphenols

Polyphenols are secondary metabolites of plants and are usually involved in the defense against ultraviolet light or aggression by pathogens. In food, polyphenols may contribute to bitterness, astringency, color, flavor, odor, and oxidative stability ( Pandey and Rezvi, 2000). Polyphenols have biological activities including anti-cardiovascular (Mattera et al.,2017), antioxidation (Eghbaliferiz and Iranshahi, 2016), antiviral ( Zhao et al., 2017; Lecher et al., 2019), antimicrobial (Gutiérrez-del-Río et al., 2018; Lima et al., 2019), anti-inflammatory (Panahi et al., 2015; Hussain et al., 2016; Pinho-Ribeiro et al., 2016; Porro et al., 2019), estrogenic (Erkkola et al., 2010; Luo et al., 2014), anti-ageing (Moussa et al., 2017; Small et al., 2018; Enogieru et al., 2018) and anticancer (Cruz-Correra et al., 2006; He et al., 2011; Brglez Mojzer et al., 2016; Kundur et al., 2019; Xiong et al., 2019; Chen et al., 2019) effects.

### Biosynthesis of polyphenols

The biosynthesis pathways of polyphenols include the shikimic acid and phenylpropanoid metabolism pathways (Chen et al., 2018). The shikimate pathway consists of seven reaction steps (Figure 1). The first enzymatic step of the shikimate pathway, 3-deoxy-D-arabino-heptulosonate 7-phosphate synthase (DAHPS), catalyzes an aldol condensation of phosphoenolpyruvate (PEP), and D-erythrose 4-phosphate (E4P) to produce 3-deoxy-D-arabino-heptulosonate 7-phosphate (Tohge et al., 2013). The two phosphorylated active compounds are synthesized in the glycolytic and pentose phosphate pathways, respectively (Kojima et al., 2015). The last step in the shikimate pathway is the formation of chorismate by Chorismate mutase (CM), which leading to aromatic amino acids, phenylalanine, and tyrosine biosynthesis, by successive reactions ( Hamberger et al., 2006; Averesh and Krömer, 2018).

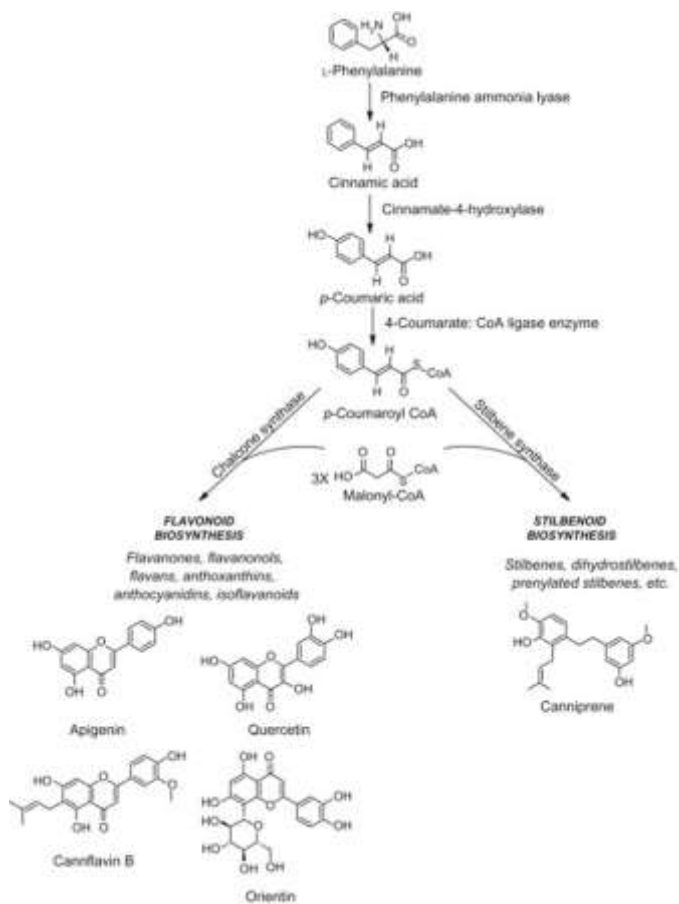
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**Figure 1.** Scheme of the shikimate pathway leading to phenylalanine and tyrosine biosynthesis. Individual metabolic intermediates starting from erythrose-4-phosphate and phosphoenolpyruvate are shown. In-boxed, the central intermediate chorismate at the branch point between tryptophan and phenylalanine/tyrosine pathways. Enzymes catalyzing individual steps are numbered as follows: (1) 3-deoxy-D-arabino-heptulosonate-7-phosphate synthase, (2) 3-dehydroquinate synthase, (3) dehydroquinate dehydratase/shikimate dehydrogenase, (4) dehydroquinate dehydratase / shikimate dehydrogenase, (5) shikimate kinase, (6) 5-enolpyruvyl shikimate-3-phosphate synthase, (7) chorismate synthase, (8) chorismate mutase, (9) prephenate aminotransferase, (10) aroclavate dehydrogenase, (11) aroclavate dehydratase, (12) prephenate dehydratase, (13) aromatic aminotransferase. ( Hamberger et al., 2006).

Subsequently, the phenylpropanoid pathway channels the carbon flow from amino acid metabolism to different branch pathways of secondary metabolism which include the synthesis of the diverse polyphenols. Phenylalanine ammonia-lyase (PAL; E.C.4.3.1.5) is a key enzyme of the phenylpropanoid pathway in plant development, and it catalyses the deamination of phenylalanine from primary metabolic pool to trans-cinnamic acid, leading to the production of secondary metabolites. In the reaction catalyzed by PAL, L-phenylalanine (L-Phe) is deaminated to form trans-cinnamate and ammonium ion

(Maldonado et al., 2006). Then, Cinnamate-4-hydroxylase (C4H) converts trans-cinnamic acid (CA) to *p*-coumaric acid (Kumar et al., 2016), it is converted in *p*-coumaroyl CoA by addition of a CoA thioester by a 4-coumarate:CoA ligase enzyme. This common high energy intermediate is used in the biosynthesis of cell wall constituents (lignins), pigments (flavonoids, antocians), and UV protectant and pest resistance compounds (stilbenoids, flavonoids, isoflavonoids, coumarins, and furanocoumarins) (Thomas and ElSohly, 2016). (Figure 2)

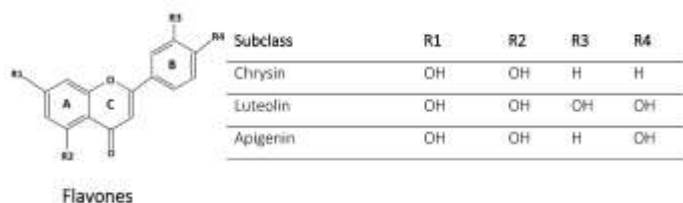


**Figure 2.** Biosynthesis of phenylpropanoids by phenylalanine (Thomas and ElSohly, 2016)

*p*-Coumaric acid can also be obtained from the deamination of tyrosine by the enzyme tyrosine ammonia-lyase (TAL)(de la Rosa et al., 2019) (Figure 3). Afterward, *p*-Coumarate can be metabolized in two different ways. It can be activated to form the coenzyme A (CoA) ester or it may be converted to other hydroxycinnamic analogues (Figure 3). The formation of *p*-Coumaroyl - CoA is catalyzed by 4-coumarate- CoA ligase (4CL). This enzyme acts in multiple substrates, activating also the other analogues. After activation, *p*-Coumaroyl – CoA can also be transformed to caffeoyl-CoA and feruloyl-CoA. At this point the polyphenol biosynthesis diverges and the enzymes



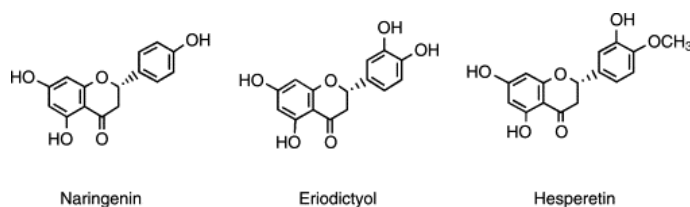
Flavones are one of the major classes of flavonoids. Flavones are frequently present in leaves, flowers, and fruits as glucosides. Celery, parsley, red peppers, chamomile, mint, and ginkgo biloba are rich sources of flavones (Panche et al., 2016). Chrysin, apigenin, rutin (glycoside), and luteolin belong to this subclass of flavonoids (Shah and Smith, 2020) (Figure 5). Besides to protecting plants from microbial diseases, flavones also possess diverse biological activities such as anti-inflammatory, anti-estrogenic, antimicrobial, anti-allergic, antioxidant, vascular, antitumor, and cytotoxic activities (Das et al., 2014).



**Figure 5.** Flavones: chemical structure, types and substitution positions in the basic skeleton (Shah and Smith, 2020)

### Flavanones

Flavanones, called dihydroflavanones, lack the double bond between carbons 2 and 3 in the C-ring of the flavonoid skeleton, which is present in flavones and flavonols (Andersen and Markham, 2005). They are widely distributed in about 42 higher plant families especially in Compositae, Leguminosae, and Rutaceae. Depending on the type of plants, they can be discovered in all of the parts-above and below ground, from vegetative parts to generative organs: branches, bark, stem, leaves, roots, flowers, fruits, seeds, rhizomes, peels, and others (Mukherjee, 2019). Flavanones, represented principally by naringenin, hesperetin, and eriodictyol (Jaganath and Crozier, 2008) (Figure 6).

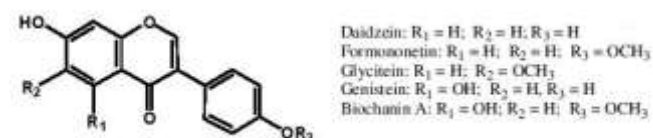


**Figure 6.** Structures of common flavanone aglycones (Jaganath and Crozier, 2008)

Many flavanones are shown to have antioxidative activity, free radical scavenging capacity, cardiovascular effects (Vasorelaxant and vasoprotective effects, act on atherosclerosis and coronary heart disease), antiviral, antiallergic and anticancer activities, inhibition of tumor development, anti-inflammatory, antimutagenic, and anti-proliferation effects (khan et al., 2014).

### Isoflavones

Isoflavones comprise a subclass of naturally occurring phenolic flavonoids and have a structure similar to estrogen (Gupta et al., 2016). In contrast to most other flavonoids, isoflavones are characterized by having the B-ring attached at C3 rather than the C2 position (Tanwar and Modgil, 2012) (Figure 7). These compounds are produced almost exclusively by the members of the Fabaceae (i.e., Leguminosae, or bean) family of the plant kingdom (Rupasinghe, 2015). Since beans, particularly soybean, are a major part of the diet in many cultures, the role of Isoflavones have, thus, a great impact on human health (Tsao, 2010). The Isoflavones are formed by amino acid phenylalanine, which reacts with malonyl CoA to become 4-hydroxycinnamoyl CoA. In the next reaction, chalcone synthase convert 4-hydroxycinnamoyl to naringenin chalcone, which is then converted by chalcone synthase and chalcone reductase to isoliquirigenin. Chalcone isomerase closes the heterocyclic ring to form liquirigenin and naringenin. The B-ring is moved from the 2-position to the 3- position by isoflavone synthase, and isoflavone dehydratase removes water to generate unsaturation in position 2,3 in the heterocyclic ring, thus forming daidzein and genistein (Rodríguez-Landa et al., 2018). Isoflavones exhibit antioxidant, anticancer, antimicrobial, anti-inflammatory, antiosteoporotic, and estrogenic properties (Dini, 2019). The main isoflavones are genistein, daidzein and glycitein (Carbonel et al., 2018).



**Figure 7.** Chemical structure of main isoflavones (Villares et al., 2011).

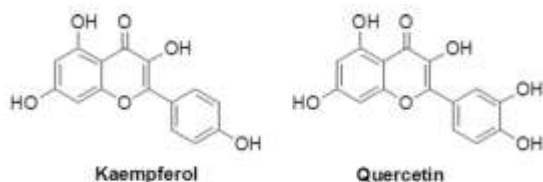
Genistein can act as a phytoestrogen in mammals and, though they are not steroids, can alter the activity of the estrogen receptor. Genistein has been shown to suppress the activity of NFκB when arachidonic acid (an omega 6 fatty acid which usually promotes inflammation) is included in the diet and to complement the activity of docosahexaenoic acid (DHA, which is usually anti-inflammatory) against breast cancer. Daidzein another isoflavone, has been shown to decrease proinflammatory cytokines and suppress chronic inflammation in obese mice (Hardman, 2014).

### Flavonols

The subclass flavonols are the most ubiquitous of flavonoids in food. The richest sources are onions, curly kale, leeks, broccoli, and blueberries (Pérez-Chabela and Hernández-Alcántara,



2018). Quercetin and kaempferol are the main representative molecules (Dabeek and Marra, 2019)(Figure 8).

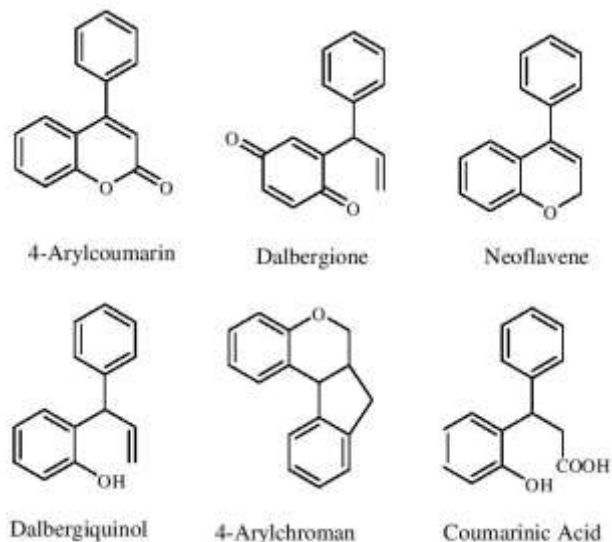


**Figure 8.** Structures of kaempferol and Quercetin (Park, 2016)

Quercetin has attracted researchers' attention for its activity against cancer prevention, chronic inflammation, and cardiovascular diseases (Durazzo et al., 2019). In addition, several patents have been recently reported on quercetin derivatives for wide therapeutic applications such as anticancer, antiaging, and as an anti-inflammatory agent (Sharma et al., 2018). Kaempferol is a natural flavonol present in different edible plants (e.g., tea, broccoli, cabbage, kale, beans, endive, leek, tomato, strawberries, and grapes). It has been described to possess anti-inflammatory, anticancer, and notably cardiovascular protective properties (Devi et al., 2015; Rajendran et al., 2014).

### Neoflavonoids

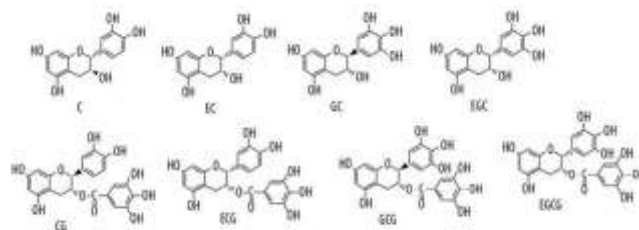
The term neoflavonoid refers to a group of C<sub>15</sub> naturally-occurring compounds that include a C<sub>6</sub>-C<sub>3</sub>-C<sub>6</sub> Carbone (1,1-diphenyl propane skeleton), structurally related to flavonoids and isoflavonoids. This term was suggested by Dr Swain T to describe the group of natural products with a 4-phenylchroman skeleton. The vast majority of known neoflavonoids have been isolated from the Fabaceae and Clusiaceae. Some are also present in the Rubiaceae (Gomathi, 2015). Neoflavonoids depending on the pattern of substitution and sources, they are categorized into four groups, namely 4-arylcoumarins (neoflavones), 4-arylcromanes, dalbergiones, and dalbergiquinols. These compounds have been found to display several health-beneficial properties. They have wide-ranging therapeutic properties, such as anti-osteoporosis, anti-inflammatory, antimicrobial, antiplasmodial, anti-androgen, anti-allergic, antioxidant, antifungal, antidiabetic, and anticancer activities (Kumar et al., 2020).



**Figure.9.** Examples of neoflavonoid (Gomathi, 2015)

### Flavanonols

Flavanonols, which are also referred to as dihydroflavonols, are the 3-hydroxy derivatives of flavanones. They lack the double bond between carbons 2 and 3 in the C ring present in flavones and flavonols (Gonçalves et al., 2018). Flavanonols exist in monomeric, oligomeric, and polymeric forms and are not glycosylated. Major sources of flavanonols are fruits, berries, cereal, nuts, chocolate, and tea (Mojzer et al., 2016). Catechin and epicatechin are two compounds among the commonest flavanonols known, sharing a distribution almost as widespread as the related flavonol, quercetin. Catechin (C), epicatechin (EC), gallocatechin (GC), epigallocatechin (EGC) and their galloyl substituted derivatives (ECG, and EGCG) (Figure 10) are usually found in plant-derived foods and food products.

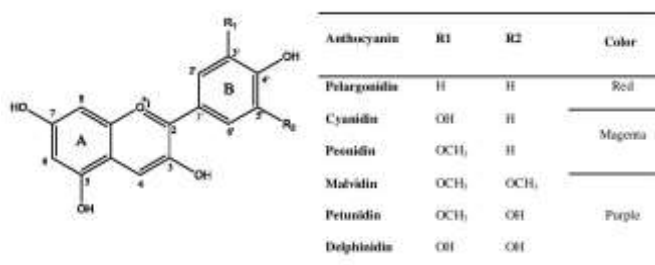


**Figure.10.** Chemical structures of the main flavanonols (He et al., 2018).

Flavanols in foods are described to possess multiple beneficial effects such as antioxidant and anticarcinogenic properties and also contribute to the sensory properties of some food products, such as astringency and color (Oliveira et al., 2013).

## I. Anthocyanins

Anthocyanins are phenolic compounds belonging to the family of flavonoids that constitute the largest group of water-soluble pigments in the Plant Kingdom. They are responsible for the red, purple, and blue colors of many fruits, vegetables, cereal grains, and flowers (Bueno et al., 2012). In plants, the anthocyanin molecule occurs as a glycoside that contains sugar (glycone moiety, i.e., mostly glucose, or xylose, rhamnose, galactose, or arabinose) and a nonsugar component (aglycone, i.e., anthocyanidin) (Ullah et al., 2019). Chemically, anthocyanins are glycosylated, polymethoxy, or polyhydroxy derived from the anthocyanidins. They are formed by an anthocyanidin molecule, that is the aglycone, to which a sugar moiety is bound by a  $\beta$ -glycosidic bond or, in some cases, by  $\alpha$ -glycosidic bond (Magaña Cerino et al., 2020). Cyanidin, delphinidin, malvidin, pelargonidin and peonidin are the most commonly studied anthocyanidins (Ullah et al., 2019) (Figure 11).

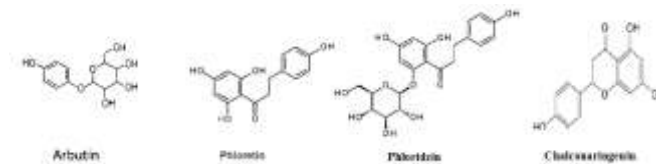


These compounds play relevant roles in plant propagation and ecophysiology, plant defense mechanisms and are responsible for the color of fruits and vegetables (Santos-Buelga et al., 2014). Also, they have been shown to act as a 'sunscreens,' protecting cells from high light damage by absorbing blue-green and ultraviolet light, thereby protecting the tissues from photoinhibition (Davies et al., 2003). Anthocyanins extracted from plants have been used as natural food additives. Food additive, E163, is one of the commercial additives extracted from fruit anthocyanin such as grape skin. It is a purple food additive used to color bakers jam, confectionaries, and beverages. It is one of the bioactive components as nutraceutical and traditional medicine. It has been traditionally used as a phytopharmaceutical, appetite stimulant, choleric agent, and for treatment of many other diseases (Khoo et al., 2017). Anthocyanins possess antidiabetic, antioxidant, anticancer, anti-inflammatory, antimicrobial, neuroprotective, and anti-obesity effects, as well as prevention of cardiovascular diseases (He et al., 2011, Khoo et al., 2017).

## II. Chalcones

Chalcones are a group of flavonoids compounds present in many fruits (citrus, apple, tomato, etc), vegetables (shallots, bean sprouts, potatoes, etc.), and also some edible plants (licorice) from our daily diet (Kłósek et al., 2017; Schnekenburger and Diederich, 2017). The term "Chalcones" was given by

Stanisław Kostanecki and Josef Tambor. They are 1,3-diphenyl-2-propene-1-one, in which two aromatic rings are linked by a three-carbon  $\alpha$ ,  $\beta$ -unsaturated carbonyl system (Jaiswal et al., 2018). The most common examples are phloridzin, arbutin, phloretin and chalconaringenin (Figure 12) (Rashad et al., 2020).



**Figure.12.** Chemical structures of the main chalcones (Li et al., 2011; Zielinska et al., 2019; Salehi et al., 2019)

Chalcones, as other flavonoids and phenolic compounds, play an important ecological role as signaling molecules in plant-microbe symbioses, being essential for plant survival. In addition, glycosylconjugated chalcones are widely distributed flower pigments, having an important role in pollination (Díaz-Tielas et al., 2016). They have also diverse biological potential, such as antibacterial, antioxidant, anticancer, anti-HIV, anthelmintic, antimalarial, antifungal, anti-inflammatory, Monoamine oxidase inhibition, antihypertensive, antidiabetic, anti-obesity, anti-neuroprotective, and hepatoprotective, anti-angiogenic and anti-leishmanial activities (Orlikova et al., 2011; Jaiswal et al., 2018; Mah, 2020).

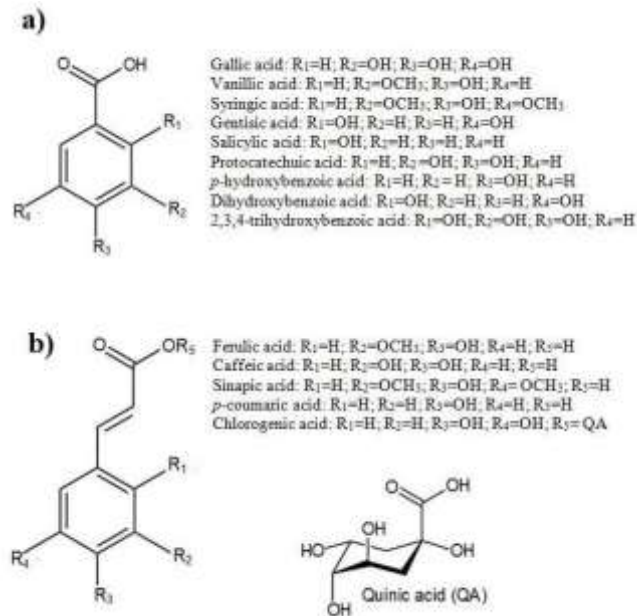
## Non-flavonoid polyphenols

The non-flavonoid metabolites include phenolic acids, lignans, stilbenes, tannins, and lignins (Orlowski et al., 2020).

## Phenolic acids and coumarins

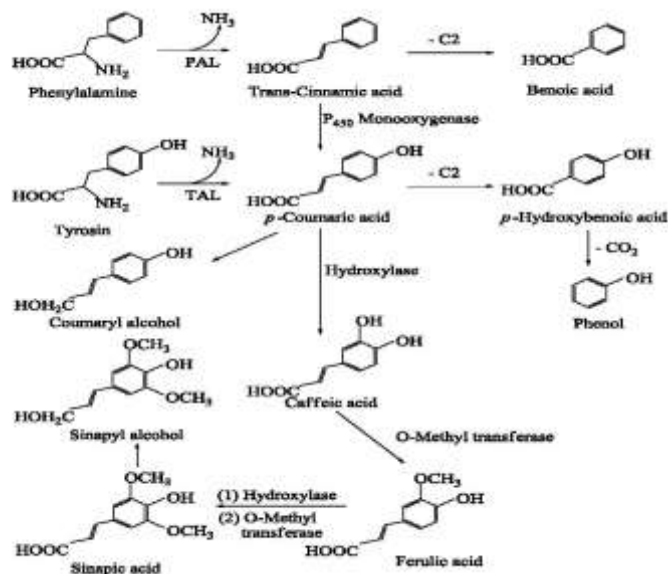
Phenolic acids and their derivatives are secondary metabolites widely spread in fruits, vegetables, and cereal grains (Das et al., 2019). The main sources are berries, cherries, apples, citrus fruits, rice bran, passion fruit, mangoes, coffee, kiwis, tea, wheat, corn, and oat flours (Klensporf-Pawlik and Aladedunye, 2017). Phenolic acids are mainly divided into two sub-groups: hydroxybenzoic and hydroxycinnamic acid (Clifford, 1999). Hydroxybenzoic acids possess a general structure derived directly from benzoic acid. Variations in structure lie in the hydroxylations and methoxylations of the aromatic cycle (Murkovic, 2003). In foods, they are usually present in the bound form as components of complex structures like lignins and hydrolyzable tannins or linked to cell walls and proteins (Liu, 2013). Protocatechuic acid, vanillic acid, syringic acid, gallic acid, and p-hydroxybenzoic acid, are the most common hydroxybenzoic acids found in vegetables (Kumar and Goel, 2019; Liu, 2004). The content of hydroxybenzoic acid (both free and esterified) of edible plants is generally very low, in except of certain red fruits, black radish, onions, and tea (Maru et al.,

2014). Structurally, hydroxycinnamic acids are hydroxy metabolites of cinnamic acid with a C6–C3 backbone (Martinez et al. 2017). Ferulic acid, caffeic acid, p-coumaric acid, chlorogenic acid, sinapic acid, and quinic acid belong to this important phenolic acid group. They are found in abundance in fruits, vegetables and cereals, and seeds of fruits (El-Seedi et al., 2012) (Figure 13).



**Figure.13.** Structures of common phenolic acids: (A) benzoic acid derivatives and (B) hydroxycinnamic acid derivatives (Singh et al., 2017)

The basic pathway for biosynthesis of phenolic acids in plants begins from sugars through to aromatic amino acids – phenylalanine, and, in some rare cases, tyrosine. The formation of trans-cinnamic acid from phenylalanine and p-hydroxycinnamic acid from tyrosine is catalyzed by phenylalanine ammonia-lyase (PAL) and tyrosine ammonia-lyase (TAL), respectively (Chavan, 2018) (Figure 14).



**Figure .14.** Biosynthesis of phenylpropanoids of the cinnamic acid family as well as benzoic acid derivatives and corresponding alcohols from phenylalanine and tyrosine; PAL: phenylalanine ammonia-lyase; and TAL: tyrosine ammonia-lyase (Albishi, 2018).

In-plant, phenolic acids have a role in growth, reproduction, and defense against environmental stress and microorganisms (Valentine et al., 2003; Elzaawely et al., 2007). Most of them are an integral part of the human diet and are also consumed as medicinal preparations (Shahidi and Ambigaipalan, 2015). Many of the health-protective effects of phenolic acids have been ascribed to their antioxidant, antiulcer, antidiabetic, cardioprotective, antimutagenic, anticarcinogenic, antiinflammatory, neuroprotective, hepatoprotective, antiaging and antimicrobial properties (Saibabu et al., 2015).

Coumarins (2H-1-benzopyran-2-one) comprise a very large class of phenolic substances found throughout the plants and are made of fused benzene and  $\alpha$ -pyrone rings (Aoyama et al., 1992). The name coumarin originates from the French term “coumarou” for the Tonka bean (Dipteryx odorata), from which coumarin was isolated for the first time, in 1820 by Vogel (Önder, 2020). They are widely distributed in nature, more than 1300 coumarins have been identified as secondary metabolites from plants, bacteria, and fungi (Iranshahi et al., 2009). They can be found in the integument of seeds, fruits, flowers, roots, leaves, and stems, although the largest concentration is generally in fruits and flowers (Martínez, 2012).

Coumarins can be subdivided into simple coumarins (benzo- $\alpha$ -pyrones syn 1,2-benzopyrone), dimer coumarins, furanocoumarins (7-oxygenated coumarins), and

pyranocoumarins (Figure 15)(Poumale et al., 2013 ). Coumarins are considered as secondary plant metabolites involved in the protection of the plant from infections, with an important role in plant biochemistry and physiology; they act as antioxidants, enzyme inhibitors, and precursors of toxic substances. Particularly, these compounds are involved in the activity of plant growth hormones and growth regulators, respiration control and photosynthesis (Loncar et al., 2020). Coumarin and its derivatives possess a wide range of biological properties such as antimicrobial, antioxidant, anti-inflammatory, anti-HIV, anticancer, anticoagulants, antihypertensive, antiviral, neuroprotective, antihyperglycemic, anticonvulsant, and antituberculosis(Ojala, 2001; Venugopala et al., 2013). Coumarins are widely used in drug production, cosmetics, agrochemicals, pharmaceuticals optical brighteners, dispersed fluorescent and laser dyes, as well as in the food industry (Mir et al., 2016).

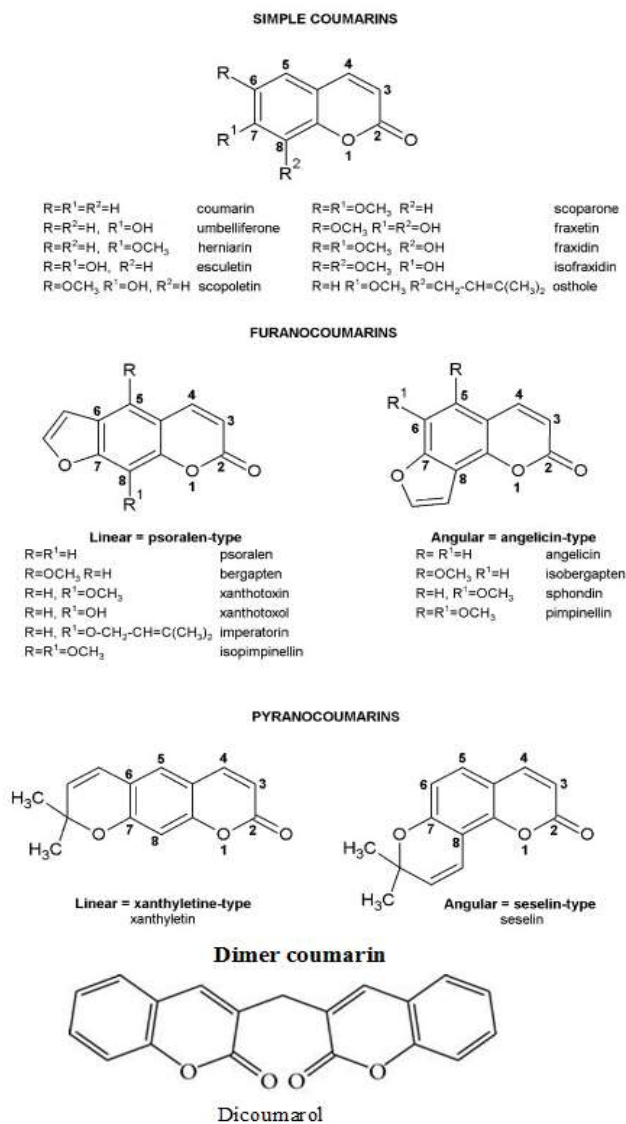
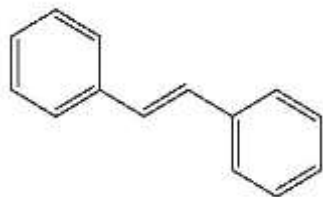


Figure .15. Examples of the main types of coumarin compounds: simple, dimer, Furano-, and pyranocoumarins (Venugopala et al., 2013; Bartnik and Facey, 2017).

### Stilbenes.

Stilbenes are phytochemicals with a small molecular weight (200–300 g/mol), a subclass of polyphenolic compounds. They are naturally found in a wide variety of dietary sources such as grapes, blueberries, and other plants (Tsai et al., 2017). Structurally, stilbenes have a basic carbon skeleton, C6–C2–C6, that contains two benzene rings linked through an ethanol or ethylene molecule (Figure 16).

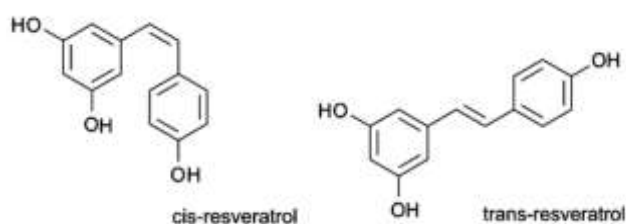




**Figure.16.** Basic structure of stilbenes (Ahmed et al., 2017).

Stilbenes have E and Z conformations each eliciting different pharmacological activities. Research revealed that the E form or trans exhibits more potent anticancer activity compared to the Z form or cis form (Khan et al., 2017). The Z-form of stilbenes has a higher antioxidant potential in animal models (Roupe et al., 2006). Stilbene and its analogues hold enormous potential importance due to their diverse spectrum of biological applications such as anticancer (Inayat-Hussain and Thomas, 2004; Hart, 1981; Roman et al., 2013; Gosslau et al., 2008; Kumar et al., 2013), antiproliferative (Jang et al., 1997; Pettit et al., 2005), antiangiogenesis (Jang et al., 1997; Pettit et al., 2005), antimicrobial (Kabir et al., 2007; Wieslaw and Bogdan, 1999; Ali et al., 1992; Boonlaksiri et al., 2000; Gao et al., 2006), antileukemic (Gao et al., 2006; Zheng and Ramirez, 1999), antioxidant (Gao et al., 2006; Cai et al., 2003; Matsuda et al., 2003), anti-inflammatory (Gao et al., 2006), anti-HIV (Wang et al., 2004; Likhitwitayawuid et al., 2005), anti herpes simplex virus (Docherty et al., 1999) and tyrosine kinase inhibitors (Thakkar et al., 1993; Giraud et al., 2008).

Resveratrol is the main representative of this group of phenolic compounds (Fay and Kussmann, 2010). It exists in both cis- and trans-isomeric forms, the trans- isomer being the most commonly found and extensively studied (Vestergaard and Ingmer, 2019) (Figure 17).



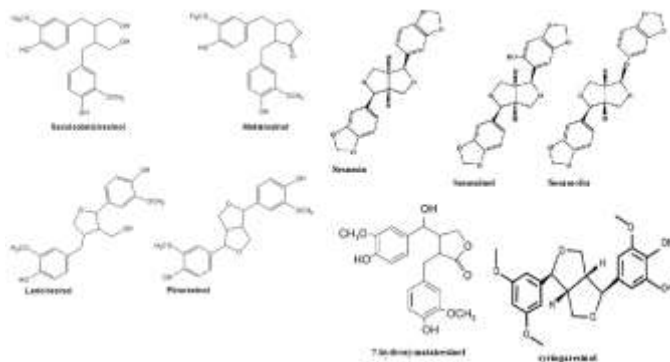
**Figure .17.** Structures of cis- and trans-resveratrol (Singla et al., 2019).

Resveratrol synthesis is induced in plants as a response to fungal infection, abiotic stresses (UV irradiation, metallic salts, methyl jasmonate) as well as to natural compounds eliciting plant defense responses or nonpathogenic rhizobacteria (Jeandet et al., 2012). Resveratrol is found in small fruits such as grapes and *Vaccinium* berries, peanuts, and in *Polygonum* species (Rimando and Suh, 2008). Resveratrol exhibit diverse beneficial health

properties, including anti-ageing, anticancer, antioxidant, antibacterial, anti-inflammatory, antiviral, cardioprotective, and neuroprotective effects (Lim and Koffas, 2010; Shan et al., 2008; Szekeres et al. 2010; Bastianetto et al., 2015).

### Lignans.

The lignans belong to a group of polyphenolic compounds containing the 2,3- dibenzylbutane skeleton. They are present in seeds, vegetable oils, cereals, legumes, fruits, and vegetables as aglycones, glycosides, esterified glycosides, or as bio-oligomers (Gerstenmeyer et al., 2013; Nabavi et al., 2013). Structurally, they are formed of two phenylpropane units joined together by at least one carbon-carbon bond between the two central  $\beta$ -carbons of the C3 chains (lignans) or by bonds other than the  $\beta$ - $\beta'$  carbon-carbon bond (neolignans) (Ferrazzano et al., 2011). The most common derivatives are: lariciresinol, pinoresinol, secoisolariciresinol, syringaresinol, matairesinol, 7-hydroxmatairesinol, sesamin, sesamol and sesamol (Nabavi et al., 2019) (Figure 18). The lignans have exhibited several potent, significant, biological activities, including anticancer, antimicrobial, antiviral, immunosuppressive, anti-inflammatory, antioxidant, and hepaprotective actions and osteoporosis prevention properties (Pilkington, 2018).

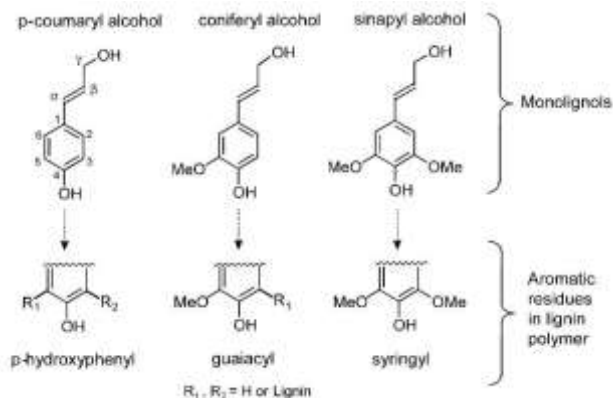


**Figure.18.** structures of the most common derivatives lignans (Corona et al., 2020; Hong and Lyu, 2013; Ide et al., 2001; Bylund et al., 2005).

### Lignins

Lignin is one of the most predominant biopolymers present in plants (Gellerstedt and Henriksson, 2008), that comprise 16–33% of wood biomass and represent the second largest organic compound after cellulose (Bujor, 2016). It is a component of all vascular plants found mostly between cellular structures but also within the cells and in the cell walls (Abhilash M and Thomas, 2016). Lignin is derived mainly from three monomers, called monolignols, from which most lignins are built: coniferyl

alcohol, sinapyl alcohol, and p-coumaryl alcohol. In the polymer, they are found as guaiacyl, syringyl, and p-hydroxyphenyl residues respectively (Holmgren, 2008) (Figure 19). These monomers are linked to each other by ether bonds, which are dominant, and/or by C-C bonds (Aho et al., 2013).

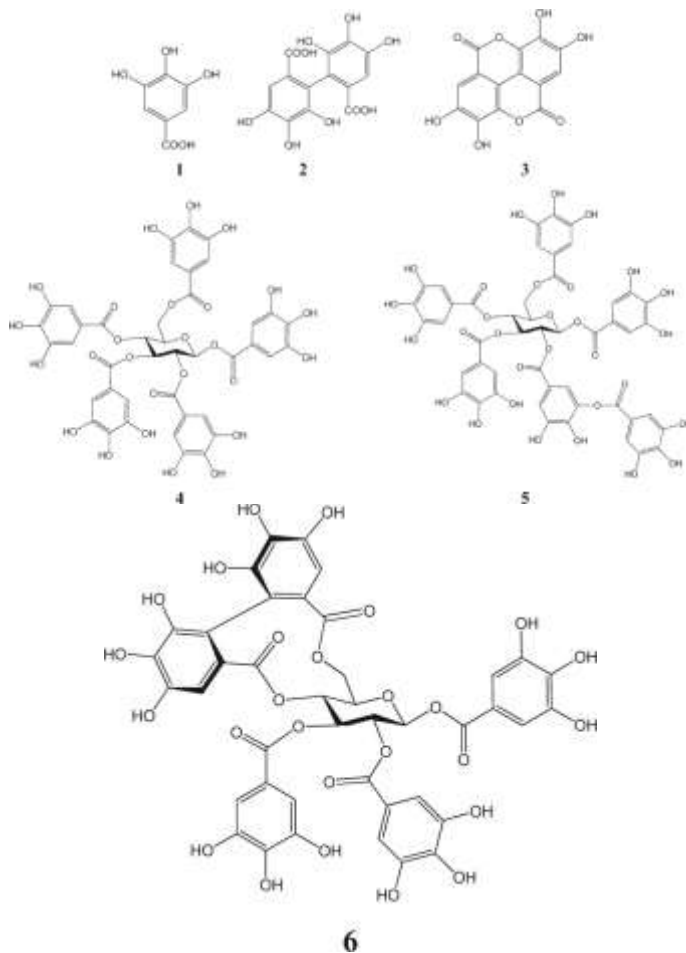


**Figure.19.** The common monolignols - and carbon number nomenclature - and their respective residues as found on the lignin polymer (Holmgren, 2008).

In plants, lignins are important because they aid water transport, strengthen the plant cell walls, protect polysaccharides in the plant cell walls from degradation, help plants to resist on pathogens and other threats, and provide texture in edible plants (Vattem and Maitin, 2015). Lignins are also important to human health because possesses multiple properties such as antioxidant, antimicrobial (Dong et al., 2011), antiparasitic (Baurhoo et al., 2008), UV absorption (Liu et al., 2014; Yu et al., 2015), anticarcinogenic (Wang et al., 2015), apoptosis-inducing antibiotic (Zemek et al., 1979), and anti-HIV (Lee et al., 2011), and it has been suggested that can be applied for stabilization of food and feed (Yang et al., 2016).

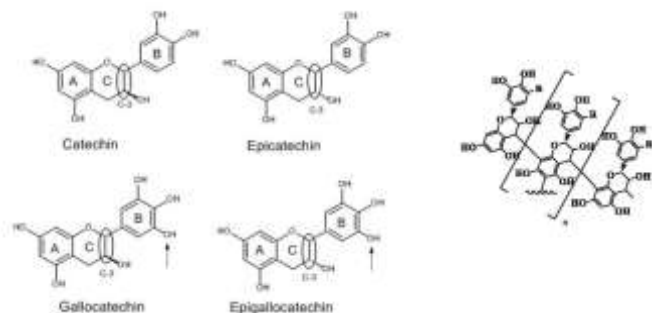
### Tannins

Tannins are polyphenolic compounds possessing astringent properties. These compounds are soluble in water, alcohol, and acetone and can coagulate proteins (Basri and Fan, 2005). They are stored in vacuoles, thus they are found in many parts of the plant, such as bark, wood, leaves, fruits, and roots (Lekha and Lonsane, 1997; Purwar, 2019). Historically, tannins have been divided into two main groups of polyphenols, hydrolysable and condensed ones, this last one is also known as proanthocyanidins (Fraga-Corral et al., 2020). Hydrolysable tannins are esters of gallic or ellagic acid linked to a polyol core, typically glucose (Naumann et al., 2017). They produce carbohydrate and phenolic acids if they are hydrolyzed by weak acids or weak bases, while on heating them with hydrochloric or sulfuric acids yield gallic or ellagic acids. (Siddiq et al., 2012).



**Figure. 20.** Characteristic structures of hydrolysable tannins: gallic acid (1); hexahydroxydiphenic acid (2); ellagic acid (3); pentagalloyl glucose (4), the basic unit of hydrolysable tannins; 2-O-digalloyl-1,3,4,6-tetra-O-galloyl- $\beta$ -D-glucopyranose (5), the example of gallotannin; tellimagradin II (6), the typical ellagitannin (Macáková et al., 2014).

The condensed tannins (also known as proanthocyanidins, PAs) are polymers that are formed by monomeric flavan-3-ols units that are connected via C-4-C-8 bonds, and sometimes through C-4-C-6 linkages. The presence of asymmetric centers at the C-2 and C-3 positions of the monomeric units has resulted in four isomers (+)- gallocatechin, (-)-epigallocatechin, (+)-catechin, and (-)-epicatechin (Figure 21) (He et al., 2008; Bule et al., 2020).

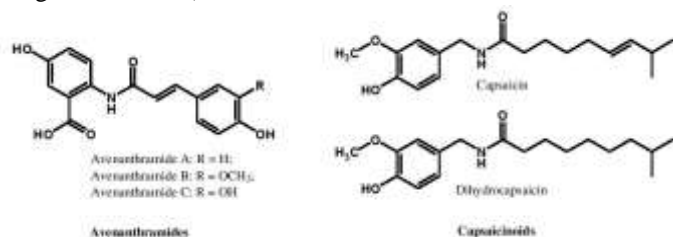


**Figure.21.** Structure of condensed tannin and its monomer (Naumann et al., 2017; Bule et al., 2020)

In plants, they provide defense against herbivores and pathogens, and protection against UV radiation (Brillouet et al., 2013). In recent years, considerable attention has been drawn to tannins and their monomers because of their potential beneficial effects on human health such as immunomodulatory and anticancer activities, antioxidant and radical scavenging functions, anti-inflammatory activities, cardio-protective properties, vasodilating and antithrombotic effects, UV-protective functions, etc (He et al., 2008; Smeriglio et al., 2017).

### Polyphenol Amides

Some polyphenols have N functional substituents. There are two subclasses of this phenolic group; capsaicinoids in chili peppers and avenanthramides in oats (Figure 22). They are reported to have strong antioxidant and anti-inflammatory properties, and they modulate the oxidative defense system in cells (Tsao, 2010; Singla et al., 2019).



**Figure .22.** Polyphenol amides (Tsao, 2010)

### Conclusion

Phenolic compounds are found in many plants and foods, such as fruits, vegetables, cereals, and beverages. This review attempts to demonstrate an overview of phenolic compounds as an important source of therapeutic molecules for pharmaceutical and medicinal applications. They have shown numerous biological activities and health benefits for the prevention and treatment of many diseases. Many studies have shown their biological activities, especially antioxidant effects, antibacterial effect, anti-cancer effect, cardioprotective effects, immune

system promoting and anti-inflammatory effects, skin protective effect from UV radiation, etc. Discussions about other polyphenol structure aspects, i.e., their synthesis in plants, and possible biological functions and implications to human health, can help establish new directions for future research. Furthermore, the synergistic of phenolic compounds' effects on biological functions would be a recommendation for further studies, as well as their mechanism of action and new biomarkers to prove their effectiveness in preventing and treating several symptoms and/or pathologies. Moreover, there is a need for future research studies of native polyphenol, which will be helpful in developing treatments to delay or prevent the progression of neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease.

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