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Evaluation of the *status quo* of polyphenols analysis: Part I—phytochemistry, bioactivity, interactions, and industrial uses

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Abbreviations: AChE, acetylcholinesterase; BPDE-2, (+)-7β-8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene; CAM, chorioallantoic membrane model; CEC, capillary electro chromatography; CNS, central nervous system; COX, cyclooxygenase; COX-1, cyclooxygenase-1; COX-2, cyclooxygenase-2; CT, non hydrolysable/condensed tannins; CYP, cytochrome P450; Cyt c, cytochrome c; DMAPP, dimethylallyl pyrophosphate; DMBA, 7,12-dimethylbenz[a]anthracene; EGCG, epigallocatechin gallate; ELISA, enzyme linked immunosorbent assay; ER, estrogen receptors; EtOAc, ethyl acetate; GRAS, generally regarded as safe; H-CM, hesperidin-treated astrocyte; HDL, high-density lipoprotein; HT, hydrolysable tannins; LDL, low-density lipoprotein; LOX, lipoxygenases; LPS, lipopolysaccharide; LTB4, leukotriene B4; MAPK, mitogen-activated protein kinase; MS/MS, tandem mass spectrometry; NDEA, N-nitrosodiethylamine; NFkB, nuclear factor kB; NK, natural killer; NNK, 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone; NOS, nitric oxide synthase; ODC, ornithine decarboxylase; *O*-Dma, *O*-desmethylangolensine; PAF, platelet activating factor; PDE, phosphodiesterase; PGE2, prostaglandin E2; RNOS, reactive oxygen and nitrogen species; RNS, reactive nitrogen species; TPA, 12–*O*-tetradecanoylphorbol-13-acetate; TXA2, thromboxane A2; UAE, ultrasound-assisted extraction; UV, ultraviolet; UV/vis, ultraviolet-visible.

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Abstract

Phytochemicals, especially polyphenols, are gaining more attention from both the scientific community and food, pharmaceutical, and cosmetics industries due to their implications in human health. In this line, lately new applications have emerged, and of great importance is the selection of accurate and reliable analytical methods for better evaluation of the quality of the end-products, which depends on diverse process variables as well as on the matrices and on the physicochemical properties of different polyphenols. The first of a two-part review on polyphenols will address the phytochemistry and biological activities of different classes of polyphenols including flavonoids, lignans and flavanolignans, stilbenoids, tannins, curcuminoids, and coumarins. Moreover, the possible interactions of polyphenols and current and potential industrial applications of polyphenols are discussed.

KEYWORDS
bioactivity, flavonoid, industrial uses, phytochemistry, plant-based food, polyphenol, possible interactions

1 | INTRODUCTION

Phytochemicals, especially polyphenols, are gaining more attention from all kinds of audiences. This is specially noticed in the scientific community and in food, pharmaceutical, and cosmetics industries due to their implications in human health, in part explained by their antioxidant properties (Faller & Fialho, 2010). Polyphenols are naturally occurring compounds found largely in fruits, vegetables, cereals, and beverages. Current literature revealed that they provide a significant protection against development of several chronic diseases like cancer, osteoporosis, diabetes, cardiovascular disease, and neurodegenerative diseases (DePace & Colombo, 2019). This is the reason explaining why polyphenols have become an emerging field of interest in nutrition in recent decades (Cory, Passarelli, Szeto, Tamez, & Mattei, 2018). In fact, in a bibliometric analysis carried out by Kan Yeung et al. (2019) regarding antioxidants, a change was observed in the scientific interest of researchers. Researchers are now more interested in antioxidant phytochemicals than in antioxidant vitamins and minerals (Yeung et al., 2019).

The present review has been written in the framework of the interest that polyphenols arouse in the scientific community. Despite the high number of articles and reviews addressing in recent years the topic polyphenols and human health, it is necessary to continuously update the state-of-the-art, since this branch of the research is a hot topic. This first of a two-part review on polyphenols systematically revisited the phytochemistry of different classes of polyphenols including flavonoids, lignans and flavanolignans, stilbenoids, tannins, curcuminoids, and coumarins. Afterward, the different biological activities of these polyphenols subclasses were addressed. The possible interactions of polyphenols and current and potential industrial applications were also discussed.

2 | PHYTOCHEMISTRY OF THE MAIN REPRESENTATIVES OF POLYPHENOLS

2.1 | Flavonoids

Flavonoids are polyphenolic secondary metabolites commonly afforded with a cetone group and normally pigments of yellow coloration from which its name is derived (from the Latin *flavus*, "yellow"). Flavonoids do not occur in animal foods; they are phytochemicals that cannot be synthesized by humans. Flavonoids represent about two thirds of the ingested polyphenols in human diet. They are generally found in the form of glycosides and sometimes as acylglycosides in fruits and vegetables. On the other hand, sulfate, acylated, and methylated molecules are not so common, and they are found in lower concentrations.

The basic structure of flavonoids is a skeleton of diphenylpropane (C6–C3–C6), with ring A and B (two benzene rings) linked by a three-carbon chain that forms a closed pyran ring (heterocyclic ring with oxygen, the C ring) with a benzenic A ring (Figure 1) (Tsao, 2010). Generally, the B ring binds to position 2 of the C ring but it can also be attached in position 3 or 4. Ring B can adopt different structural features and the three rings can undergo

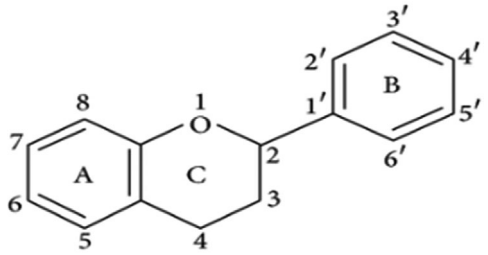


FIGURE 1 Basic structure of flavonoids

glycosylation and hydroxylation. All of this contributes to the wide variety of polyphenol structures.

Several subgroups can be found within flavonoids: flavones; flavonols; flavanones; flavanonols; flavanols, flavan-3-ols, or catechins; isoflavonoids; anthocyanins; chalcones/coumestans. These present different structural characteristics around the heterocyclic oxygen ring.

-*Flavones* present a double bond between positions 2 and 3 and a ketone in position 4 of the C ring.
-*Flavonols* present a hydroxyl group in position 3 of the C ring, which can also be glycosylated.
-*Flavanones* are also called dihydroflavones. The only structural difference between flavanones and flavones is the fact that flavones have the C ring saturated while flavanones have a double bond between positions 2 and 3 of the C ring.
-*Flavanonols* are also called dihydroflavonols, and they are 3-hydroxy derivatives of flavanones.
-*Flavanols* are also called catechins or flavan-3-ols because the hydroxyl group is almost always bound to position 3 of the C ring.
-*Isoflavonoids* have B ring attached in position 3 of the C ring, while the other flavonoids have the attached in position 4 and can be subdivided according to the structural features of the C ring. This subclass of flavonoids is described in more detail in Section 2.1.1.
-Anthocyanidins are flavylium cations, generally present as chloride salts. This subclass of flavonoids is responsible for giving colors to plants. *Anthocyanins* are glycosides of anthocyanidins. Generally, sugar units are bound to position 3 of the C ring and they are frequently conjugated with phenolic acids (e.g., ferulic acid). Anthocyanins' color is dependent on acylation and methylation at the hydroxyl groups on the A and B rings and on the pH.
-*Chalcones* present C ring-open and they are also classified as flavonoids because they present synthetic pathways similar to flavonoids

Some of the main representatives' flavonoids are listed in Table 1. The biosynthesis of flavonoids continues the metabolic route of the phenylpropane, which from the amino acid phenylalanine yields cumaryl-SCoA that, together with the malonyl-CoA, produces a group of substances called chalcones that constitute the skeleton for the biosynthesis of all flavonoids.

Most of flavones are present in herbs, isoflavonoids in legumes, flavanones in citrus fruits, flavonols in all fruits and vegetables, and anthocyanins and catechins in fruits (Peterson & Dwyer, 1998).

2.1.1 | Isoflavonoids

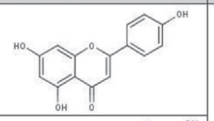
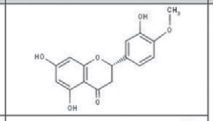
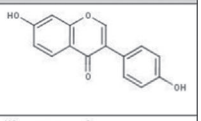
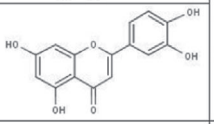
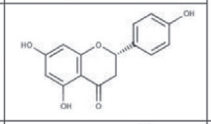
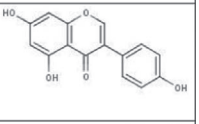
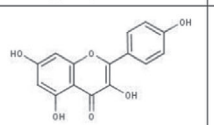
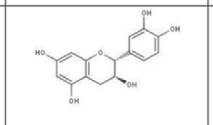
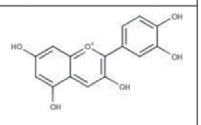
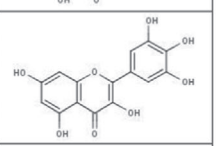
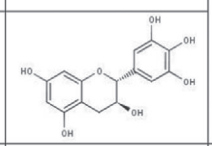
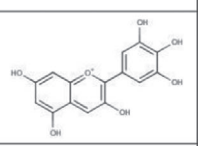
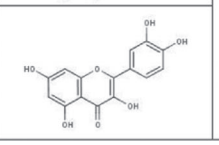
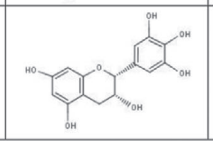
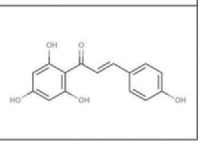
Isoflavonoids represent a structural variant of flavonoids in which the aromatic ring derived from shikimate has shifted to an adjacent carbon. The 3-phenyl chromane skeleton derives, in fact, from the 2-phenyl chromane flavonoid system through the 1,2 transposition of an aryl. This transposition is carried out by an enzyme that transforms the flavanones liquiritigenin and naringenin into daidzein and genistein isoflavones, respectively, through intermediate hydroxyflavons.

Isoflavonoids are secondary metabolites characteristic of the Leguminosae family. Despite the limited presence in plants, the structural variability of isoflavonoids is very wide and is due to the substitution pattern of rings A and B (phenolic, glycosidic, methoxyl, isoprenyl groups, etc.).

Isoflavonoids can be subdivided into subgroups depending on the oxidation level of the 3-phenyl-chromane skeleton:

- Isoflavones. This is the largest group, with over 400 known aglyons. They have estrogenic activity and for this reason are called phytoestrogens.
- Isoflavans. They show biological properties superimposable to those of isoflavones.
- Isoflavanons. They are much rarer than isoflavones. Isolated almost always in racemic mixtures, they originate very often when plants (Leguminosae) are attacked by fungi or insects (phytoalexin compounds with fungicidal properties).
- Rotenoids. They are a type of isoflavonoids with an extra C atom in an additional heterocyclic system, forming the oxidative cyclization of a 2′-methoxyisoflavone. They are powerful insecticides and fish toxins because they interfere with oxidative phosphorylation. They are harmless to mammals unless they enter the blood stream, being metabolized rapidly upon ingestion (Dewick, 2009).
- Pterocarpans. They are found in various plant products formed by a cis-benzofuranyl-benzopyran heterocyclic system that derives from a basic isoflavonoid skeleton

TABLE 1 Some of the main representative flavonoids. ChemIDplus advanced (http://chem.sis.nlm.nih.gov/chemidplus/)

Class of flavonoids	Some examples	Chemical structure	Class of flavonoids	Some examples	Chemical structure	Class of flavonoids	Some examples	Chemical structure
Flavones	Apigenin		Flavanones	Hesperetin		Isoflavones	Daidzein	
	Luteolin			Naringenin			Genistein	
Flavonols	Kaempherol		Flavan-3-ols	(-)-Catechin		Anthocyanins	Cyanidin	
	Myricetin			(+)- Gallocatechin			Delphinidin	
	Quercetin			(-)-Epigallocatechin		Chalcones	Naringenin chalcone	

with an ethereal link between positions 4 and 2′ (Luckner, 1990). The antifungal and antibacterial activity associated with most of these compounds confirms their function in plants as phytoalexins. For some of them the ability to inhibit the reverse transcriptase of HIV-1 and cytotoxic effects in HIV-1 cell cultures has also been reported.

- Coumestrans. They represent a completely oxidized version of the pterocarpans. They show powerful estrogenic activity, like isoflavones.
- Coumarans chromones and chromenes. They derive from 2-hydroxyisoflavones and 2-hydroxyisoflavans.

In plants, isoflavonoids are generally found in the form of glycosides and in order to be absorbed and biologically active, they must be metabolized and activated by intestinal bacterial flora after their ingestion; in fact, isoflavonoids are subject to hydrolysis and demethylation to obtain free aglycones, demethylated products, and other metabolites (Pathak et al., 2018). The main isoflavones undergo the following metabolic processes: Biochanin A and formononetin are demethylated giving origin to genistein and daidzein, respectively. Daidzein undergoes a transformation by the bacterial flora to obtain isoflavan equol (7-hydroxy-3 (4′-hydroxyphenyl) chromane) (about 70%) and *O*-desmethylangolensine (*O*-Dma) (5% to 20%) (Adlercreutz, 2002). Other intermediates of the daidzein that are formed during these processes are dihydrodaidzein, 4-hydroxy, and dehydroequol (Pathak et al., 2018). Genistein is metabolized to dihydrogenistein, then to 6′-hydroxy-*O*-Dma and to a compound that does not exhibit estrogenic activity such as *p*-ethylphenol (Ibarreta & Daxenberger, 2001; Pathak et al., 2018).

Antibiotic intake (effect on the microflora), cholelithiasis, surgical procedures, high-fat diet can limit the metabolization and, therefore, their activation.

The amount of phytoestrogens produced at the intestinal level varies according to diet and individuals and this would explain the different blood concentration of the respective metabolites and the different biological responses that are observed with the same isoflavonoid supplementation.

Flavonoids are widely distributed in the plant kingdom. However, isoflavonoids distribution is almost restricted to plants belonging to the Papilionaceae, subfamily of the Leguminosae, also known as Fabaceae. They are found, in particular, in soybeans (*Glycine max* (L.) Merr.) but are also common in other legumes such as beans, peas, beans, chickpeas, lentils, and in whole grains such as wheat, rice, barley, rye, and oats. These foods represent the main sources of isoflavonoids in the human diet.

Their presence was also found in peanuts (*Arachis hypogea L.*), clover (*Trifolium subterraneum* L.) belonging to the Leguminosae family (Ibarreta, & Daxenberger, 2001), and in Cuban and Brazilian propolis samples (Piccinelli et al., 2011).

Other food sources of isoflavonoids are seed oil, such as sunflower seed oil (*Helianthus spp., Asteraceae*), and walnuts (*Juglans nigra* L., Juglandaceae). These compounds have also been found in the Iridaceae and Euphorbiaceae families.

2.2 | Lignans and flavonolignans

Lignans are a class of plant secondary metabolites belonging to the group of diphenolic compounds and they have a dibenzylbutane skeleton. They can be used in pharmaceutical, food, cosmetics, and agricultural industries (Durazzo, Turfani, Azzini, Maiani, & Carcea, 2013) due to their antioxidant and anti-inflammatory activities (Landete, 2012).

In 1936, Haworth has described the term lignan as a group of phenylpropanoid dimers in which C6–C3 units are linked by the central carbon of their propyl side chains (Umezawa, 2003; Willför, Smeds, & Holmbom, 2006). Lignans can be classified into eight subgroups according to the way the oxygen is incorporated into the skeleton and the cyclization pattern: (1) furofuran (such as pinoresinol, medioresinol, syringaresinol, lariciresinol, and sesamin), (2) furan, (3) dibenzylbutane (such as secoisolariciresinol), (4) dibenzylbutyrolactone (such as matairesinol), (5) aryltetralin, (6) arylnaphthalene, (7) dibenzocyclooctadiene, and (8) dibenzylbutyrolactol (Umezawa, 2003; Whiting, 1985).

These compounds are found in diverse species in the plant kingdom including members of pteridophytes, gymnosperms, and angiosperms (Pilkington, 2018). Lignans have been isolated from members of angiosperms belonging to Asterales, Sapindales, Aristolochiales, Piperales, Laurales, Scropholariales, Lamiales, Malvales, Malpighiales Solanales, Apiales, and Magnoliales (Umezawa, 2003). Up to date, lignans have been only found in higher plants such as *Linum usitatissimum* L. (flax seed), *Piper cubeba* L., *Saururus chinensis* (Lour.) Baill, *Wikstroemia scytophylla* Diells, *Sesamum indicum* L.

Some compounds are genetically related to neolignans or true lignans, but they bear some features not discerned in conventional lignans. These compounds or group of compounds have been entitled "non-conventional lignans," including coumarinolignans, flavonolignans, and stilbenolignans (Begum, Sahai, & Ray, 2010). Flavonolignans are flavonoids derived from two phenylpropanoid units and presenting an additional structural part. C–C or C–O linkages of the C_6C_3 unit to the flavonoid nucleus can be in different positions, providing dioxane, furan, cyclohexane rings, or simple ether side chains (Csupor & Csorba, 2016). Generally, these compounds contain several chiral centers, so they usually occur in the form of stereoisomers in nature (Csupor & Csorba, 2016).

Flavonolignans have been isolated from plants belonging to Asteraceae, Berberidaceae, Chenopodiaceae, Flacourtiaceae, Fabaceae, Poaceae, and Scrophulariaceae species (Begum et al., 2010). Silybin (synonyms: silybinin, silibinin) was isolated by Pelter and Hänsel in 1986 and corresponds to the first identified component of the flavonolignan complex of "milk thistle" (*Silybum marianum*) (Pelter & Hänsel, 1968). To date 23 compounds were identified from this species (Begum et al., 2010).

2.3 | Stilbenoids

Stilbenoids are a group of naturally occurring phenolic compounds found in various plants such as grapes, berries, and other medicinal plants (Rivière, Pawlus, & Mérillon, 2012). Stilbenes are synthesized by plants in response to various stresses and are derived from the general phenylpropanoid pathway (Jeandet et al., 2010). They are a type of phytoalexin used by plants as protection against pathogens. 1,2-diphenylethylene is the basic chemical skeleton structure of stilbene compounds. Stilbenoids exist as monomers or oligomers. They may also be found free (aglycone) or conjugated as glucosides (Shen & Wang, 2009). The most popular and maybe the most widely studied is resveratrol (3,5,4′-trihydroxy-*trans* stilbene), which is found in *Vitis* species (grapes), red wine, and other plant species (López, Martínez, Del Valle, Orte, & Miró, 2001). Pterostilbene (*trans*-3,5-dimethoxy-40-hydroxystilbene) is an analog of resveratrol and is found in plant species such as *Vitis, Vaccinium* species (blueberries), and *Pterocarpus marsupium* Roxburgh (Rimando, Kalt, Magee, & Dewey, 2004). Gnetol (*trans*-2,6,30,50-tetrahydroxystilbene) is also a stilbenoid found in species of the genus *Gnetum* (Akinwumi, & Bordun, 2018). Piceatannol (*trans*-30,40,3,5-tetrahydroxystilbene) is commonly found in white tea, rhubarb (*Rheum* species), grapes, berries, and passion fruit (*Passiflora* species) (Seyed, Jantan, Bukhari, & Vijayaraghavan, 2016). It is a metabolite of resveratrol, produced by the enzyme CYP1B1 in humans (Potter et al., 2002). The isomer of hydroxylated resveratrol, oxyresveratrol, is found in the heartwood of *Artocarpus lakoocha* and in the bark of *Morus alba* (Likhitwitayawuid, Sritularak, Benchanak, Lipipun, & Mathew, 2005).

2.4 | Tannins (hydrolysable tannins [HT], condensed tannins [CT], flavono-ellagitannins, phlorotannins)

Tannins are a heterogeneous phenolic compounds group with high molecular weight. They have capacity to form reversible and irreversible complexes with polysaccharides (cellulose, hemicellulose, pectin, etc.), proteins (mainly), nucleic acids, alkaloids, and minerals, among others (Frutos, Hervas, Giraldez, & Mantecon, 2004). Tannins classification was classically based on their resistance to hydrolysis in the presence of the enzymes tannases or hot

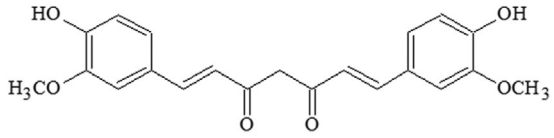


FIGURE 2 Chemical structure of curcumin

water. As a result, tannins were grouped as HT and nonhydrolysable/CT (Chung, Wong, Wei, Huang, & Lin, 1998; Sieniawska & Baj, 2016). HT have a central polyhydric alcohol group and hydroxyl groups, which are esterified by gallic acid (gallotannins) or hexahydroxydiphenic acid (ellagitannins). CT, so-called proanthocyanidins, usually present higher molecular weight than HT (1,000 to 20,000 Da vs. 500 to 3,000 Da) and they are nonbranched polymers of flavonoid units (flavan-3-ol, flavan-3,4-diol) (Mueller-Harvey I., 1999). In recent years, tannins are categorized according to their structural characteristics into four major groups: gallotannins, ellagitannins, complex tannins, and CT (Sieniawska & Baj, 2016).

Tannins are found in almost all parts of plants including the wood, leaves, bark, fruit, roots, plant galls, and seeds (Sieniawska & Baj, 2016). In stem tissue, they are often found in the layer between the cortex and epidermis and in the secondary phloem and xylem (Sieniawska & Baj, 2016). CT are synthesized and stored inside tannosomes, a chlorophyllous organelle enclosed within tonoplasts in the vacuoles. Inside tannosomes, CT do not interact with proteins and do not interfere with plant metabolism. They act and engender certain metabolic effects only after cell breakdown (Brillouet et al., 2013).

Flavono-ellagitannins, also called complex tannins, are a result of the complexation of a flavonoid with an ellagitannin through a carbon–carbon linkage. Two of them, Mongolicins A and B, were isolated from the bark of *Quercus mongolica var. grosseserrata* (Ishimaru et al., 1988).

It is interesting to report that there are marked differences in structures of terrestrial polyphenol compounds compared to marine polyphenols (phlorotannins). Flavonoids and gallic acid can be regarded as building blocks of terrestrial polyphenols (Sithranga Boopathy, & Kathiresan, 2010). Phlorotannins are phloroglucinol-based compounds reported only in brown algae, with a wide number of bioactivities and that present chains of 1,3,5-trihydroxybenzene with a vast range of molecular weights (126 to 65,000 Da) (Sanjeewa, Kim, Son, & Jeon, 2016).

2.5 | Curcuminoids

Curcumin (Figure 2), or diferuloylmethane, is a food dye (E100) imparting yellow color to preparations.

Curcumin is the main biologically active component of *Curcuma longa* L. (Zingiberaceae), from which the curcumin is extracted and concentrated. Desmethoxy curcumin and bismethoxy derivatives are also present in varying proportions. Curcuminoids are also present in lower amounts in other species of turmeric. Turmeric contains bis desmethoxyicurcumin (usually <5%) and desmethoxyicurcumin (typically 10% to 20%). Asian cultures have been using curcumin for centuries. For example, some Indian medicinal practices used curcumin to treat anorexia, coughs, rheumatism, and other diseases (Alok et al., 2014). Traditional Chinese medicine uses curcumin to treat diseases that are accompanied by abdominal pain while Hindu medicine uses it for sprains and swelling.

The chemical structure of curcumin was identified in 1913 and it presents two-feruloil chromophores attached by a methylene group. Its ultraviolet (UV) maximum light absorption occurs at 425 nm. Curcumin degrades in 30 min to vanillin, ferulic acid, feruloylmethane, and *trans*-6-(40-hydroxy-30-methoxyphenyl)-2,4-dioxo-5-hexanal, at basic pH. Interesting properties of curcumin are due to the symmetrical connection of two aryl rings via ortho-methoxy phenolic groups in conjugation via a beta-diketone. The beta-diketone is also responsible for the intramolecular transference of the hydrogen atom that originates keto-enol tautomeric and different conformations (Priyadarsini, 2009).

In nonpolar and aprotic solvents, nuclear magnetic resonance (NMR) studies showed that curcumin exists in the enol form as a result of intramolecular transfer of hydrogens (Payton, Sandusky, & Alworth, 2007).

Curcumin is stable in aqueous alcoholic solutions at low pH, but at basic pH undertakes hydrolysis and chemical degradation. Curcumin also significantly degrades in the presence of a phosphate buffer, under physiological conditions of pH. When exposed to sunlight, it undergoes photodegradation originating degradation products, including cinnamaldehyde, benzaldehyde, benzocalcone, and flavanone. Curcumin has three ionizable protons, one of the enol form and two of the phenolic OH groups (Figure 3**),** therefore, three acidity constants were estimated for curcumin (Payton et al., 2007).

2.6 | Coumarins

Coumarins (1, 2H-chromen-2-one or 2H-1-benzopyran-2-one) are phenolic compound members of the hydroxycinnamic acids and characterized by a C6–C3 carbon skeleton, mainly synthesized by plants, although they can also be found in some microorganisms (Zhao, Liu, Proksch, Yu, & Lin, 2016). Coumarins have been found in the seeds, roots, leaves, and fruits of hundreds of plant species from more

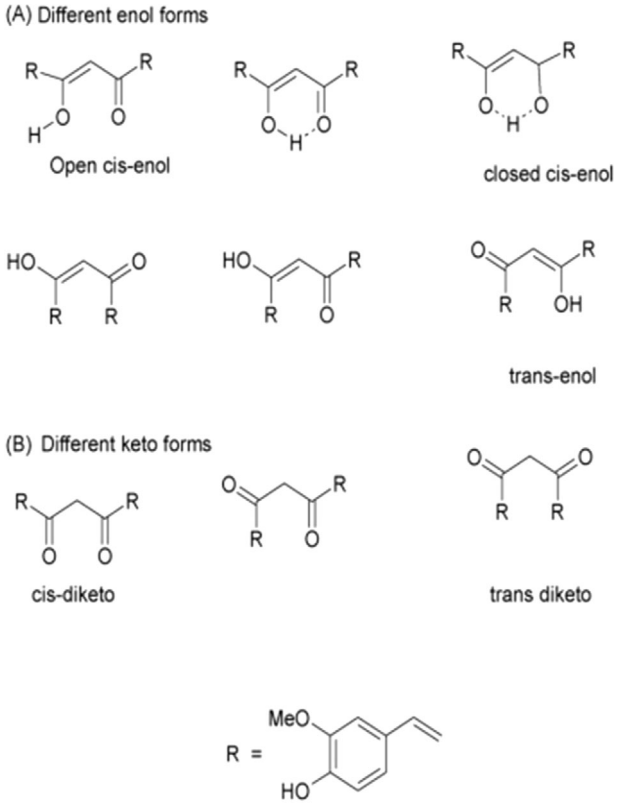


FIGURE 3 Enol and keto forms of curcumin

than 40 different families with Umbelliferae, Asteraceae, and Rutaceae being the highest source of these compounds (Matos et al., 2015).

Coumarins are abundant in several essential oils such as cinnamon bark oil or lavender oil, but also can be found in other species that are commonly part of the diet such as diverse berry fruits, green tea, carrots, celery, and members of the genus *Citrus* (Jain, & Joshi, 2012). This family of compounds comprises a wide number of benzopyrones (1,2-benzopyrone or 2H-1-benzopyran-2-one) synthesized as a defense against pathogens and/or soil iron chelators (Sarker, 2017). Within this group, coumarin was the first member of the group isolated in 1820 from the Tonka bean (*Dipteryx odorata*; Fabaceae) or in French "coumarou" by Vogel A., and is the one that gives the name to the whole family (Vogel, 1820). However, most of the coumarins found in plants are characterized by oxygenation in C7, with the initial compound being 7-hydroxycoumarin, also known as umbelliferone, because it was isolated for the first time from the Umbelliferae family (Sarker, 2017).

The group of coumarins has a high structural diversity and its members can be classified into four different subclasses: simple coumarins (hydroxy-, alkoxy-, methylene dihydroxy coumarins, and their glycosides derivatives), furanocoumarins (psoralen derivatives and angelicin derivatives), pyranocoumarins, and pyrone-substituted coumarins (Tejada et al., 2017). All members of coumarins share the same biosynthetic pathway that is derived from the metabolism of phenylalanine, which is formed through the shikimate biosynthetic pathway and later by the action of phenylalanine ammonia lyase is transformed into cinnamic acid (Vogt, 2010). Although coumarin derives from cinnamic acid in a process that involves the ortho-hydroxylation and lactonization of this compound, most of the compounds from this group derive from *p*-coumaric acid ((E)-4-hydroxycinnamic acid) (Vogt, 2010). Enzymatic oxidation occurs from *p*-coumaric acid to produce 2-hydroxy-*p*-coumaric acid (Stefanachi, Leonetti, Pisani, Catto, & Carotti, 2018). In the next step a glucidic residue is added in C2 generating a 2-glucoside that is subsequently isomerized to give rise to its (Z)-diastereomer. Next, the ring closes forming the Umbelliferone (Stefanachi et al., 2018). Furanocoumarins are characterized by the presence of a furan ring fused to the coumarin skeleton and, depending on how they join, various angular and linear structures will be formed. The synthesis process starts by binding dimethylallyl pyrophosphate (DMAPP) to umbelliferone forming a prenylated intermediate in position C6 or C8 to give rise to linear or angular furanocoumarins, respectively (Sarker, 2017). The synthesis of pyranocoumarins is similar to that of furanocoumarins, with the difference that the ring that is formed from the prenyl group is a pyran ring. Finally, the pyrone-substituted coumarins are those structures that present other modifications and/or substitutions on the pyrone ring, generally in position C3 or C4 (Lacy, & O'Kennedy, 2004).

3 | BIOLOGICAL ACTIVITIES

3.1 | Flavonoids

Flavonoids show a wide spectrum of functions in the plants, mainly as pigments of yellow colors in the petals of flowers with the function of attracting pollinating insects, or blue colors (anthocyanins) with the function of receiving certain wavelengths, that allow the plant to recognize the photoperiod. Many of these flavonoids are also involved in the UV filtration protection of plants.

In this sense, this type of compound has wide pharmacological activities in *in vitro* models such as antioxidant, anti-inflammatory, antiallergic, antibiotic, and anticancer. On the other hand, in *in vivo* models it was not possible to demonstrate either the antioxidant activity or a direct link showing them to be effective against cancer. Some studies seem to indicate that a rich diet in flavonoids can diminish this risk but without statistical significance.Therefore, under this premise, we will define the different

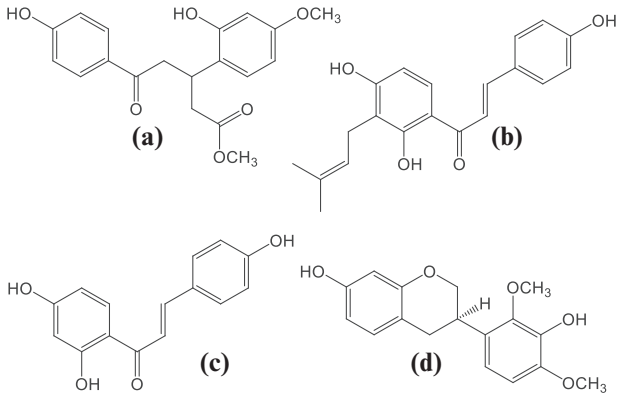


FIGURE 4 Chemical structures of novel flavonoids such as astradsurnin (a). 4,20,40-trihydroxy-30-prenylchalcone (b), 4,20,40-trihydroxychalcone (c), (3R)-7,30-dihydroxy-20,40-dimethoxyisoflavan[(R)-mucronulatol] (d)

pharmacological activities of several types of flavonoids that exist in nature under certain parameters of structure activity, bioavailability, cytotoxicity, and selectivity in the therapeutic action.

On the basis of the reported background, from 2009 until 2018 different biological activities of flavonoids have been mentioned, and they are derived from natural sources as well as from synthesized substances with promising pharmacological properties. Thus, the development of a simple and fast method for determining total flavonoids and identifying the antioxidant and antitumor activities of the extracts in the roots of *Flemingia philippinensis* was reported (Li, Lu, & Bian, 2015). In this sense, this paper reports the total flavonoid content of 19 extracts of *F. philippinensis* collected from different origins in China and obtained by ultrasonic-assisted extraction. Flemiphilippin A, auriculasin, dorsmanins I, and 5,7,3′,4′-tetrahydroxy-6,8-diprenylisoflavone showed varying results according to the DPPH radical scavenging assay. Flemiphilippinin A exhibited antitumor activity with inhibition up to 91% against human lung epithelial (A-549), human hepatocellular carcinoma cell (BEL-7402), and human ileocecal adenocarcinoma cell (HCT-8) (Li et al., 2015).

An interesting study was presented where some biological components from pathogenic-infected *Astragalus adsurgens* with an activity-guided purification process were identified (Chen et al., 2012). Consequently, 15 flavonoids were obtained by using ethyl acetate (EtOAc) fraction and identified as astradsurnin (Figure 4A), a new chalcone derivative, together with 14 known flavonoids (Figure 4B). These compounds were assessed for antibacterial activities against five bacteria and cytotoxic activities against two selected cancer cells (Figure 4). Some of them such as 2′,4′-dihydroxy-2,3-dimethoxychalcone (Markham & Ternai, 1976, Figure 4C), and 2′,4′-dihydroxy-4-methoxychalcone[isoliquiritigenin 4-methyl ether] (Dhar & Gupta, 1971, Figure 4D) were the most active against *Escherichia coli*, *Bacillus cereus*, *Staphylococcus aureus*, *Erwinia carotovora*, and *Bacillus subtilis* (Chen et al., 2012).

It must be noted that phenolics and flavonoids can be isolated from several natural sources and their biological activities related to certain active molecules. Thus, methanolic extract isolated from *Nitraria retusa* yielded some important flavonoids including isorhamnetin, isorhamnetin-3-*O*-glucoside, isorhamnetin-3-*O*-rutinoside, and isorhamnetin-3-*O*-robinobioside. The activities of these flavonoids were compared with model flavonoids (isoquercitrin, quercetin, and rutin) and aglycon compounds were more active than their glycosylated derivatives. According to the authors of this research, isorhamnetin-based flavonoids presented higher antiproliferative activities than quercetin-based ones, while similar antioxidant properties were observed (Salem et al., 2010). Many natural sources from Europe, Central Asia, and China have herbaceous perennial plants belonging to the Asteraceae family. Such plants include Sandy everlasting (*Helichrysum arenarium* (L.) Moench), where their flowers have a long tradition in European ethnomedicine being used as a cholagogue, choleretic, hepatoprotective, and detoxifying herbal drug. Moreover, the activities of naringenin, one of the main flavonoids of *H. arenarium* were studied (Pljevljakusic, Bigovic, Jankovic, Savikin, & Jelacic, 2018). However, there are no clinical data of this type of extracts, though it is mentioned that phenolic compounds such as flavonoids can be responsible in the treatment of gallbladder disease (Pljevljakusic et al., 2018).

Considerable differences among flavonoids were found in what regards to the protection against apoptosis in cell death models, a process in which cytochrome c (Cyt c) plays a key role (Lagoa, Samhan-Arias, & Gutierrez-Merino, 2017). In this sense, some flavonoids presented a Cyt-reducing capacity similar to or higher than ascorbate. Kaempferol, quercetin, myricetin, epigallocatechin-gallate, cyanidin, malvidin, and luteolin were found to have this biological property (Figure 5). However, other phenolic compounds including kaempferol 3(O)- and 3,4′(O)-methylated forms, naringenin, apigenin, and chrysin, had a negligible reducing capacity. With this information, the authors conclude that small differences in the chemical scaffold of these phenolic compounds originates very different biological activities (Lagoa et al., 2017). There are studies with biocatalytic synthesis of certain types of flavonoids with wide biological activities such as antibacterial, antioxidant, among others. The improvement of the lipophilic nature of the glycosylated flavonoids has been suggested to be due to the enzymatic acylation of natural polyphenols with fatty acids or other acyl

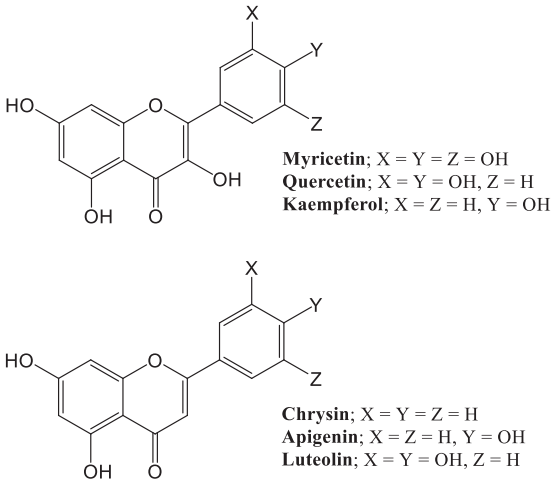


FIGURE 5 Chemical structures of flavonols and flavones

donors. Flavonoids acylation with different acyl donors may also impart beneficial properties to these molecules, such as improved of the antioxidant activity and penetration through the cell membrane. Moroever, the chemical methods for the flavonoid esters synthesis lead to the formation of side products and the simultaneous decomposition of the flavonoids. However, this type of biocatalytic synthesis of flavonoids with lipase is an interesting method to obtain active molecules with different polar substituents (de Araujo et al., 2017).

In this sense, another article has identified the glycosylation of flavonoids, which allows to improve the pharmacokinetic properties of these derivatives. This novel synthetic process could originate great diversity of compounds but the yield is low. *Saccharomyces cerevisiae* is a GRAS (generally regarded as safe) organism, with the appealing capacity of producing flavonoid glucosides. The authors reported that the engineered yeast harboring flavonoid glucosyltransferases (SbGT) with a deletion of glucosidases have produced more flavonoid glucosides than the strains that did not present a deletion of glucosidases (Wang et al., 2016).

In 2015 a group of researchers (Gacche et al., 2015) has published a study on flavonoids (flavones, flavonones, and flavonols) with antiangiogenic, cytotoxic, antioxidant, and cyclooxygenase (COX) inhibitory activities. To study the biological effects of these flavonoids, *in vivo* chorioallantoic membrane model (CAM) was used together with computational methods such as in silico docking to calculate the different atomic interactions and to design novel and active flavonoid derivatives. Furthermore, this research describes the cytotoxicity of flavonoids against selected cancer cell lines using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) cell viability assay (Gacche et al., 2015). Flavonoids can affect inflammation. In fact, Ribeiro, Freitas, Lima, and Fernandes (2015) described that the anti-inflammatory property of some flavonoids is novel and selective.

On the other hand, afzelin, kaempferitrin, and pterogynoside (Figure 6) are interesting glycoside flavonoids, acting on reactive oxygen species (ROS), especially as scavengers of the superoxide anion. However, it has been demonstrated that these compounds promoted the death of neutrophils as a cytotoxic action. The results of this research promote the design of this type of polar compounds with a glycoside moiety. The authors suggest that their radical scavenging and antioxidant properties might have potential applications in the food and health industries (Vellosa et al., 2015).

Flavonoids can have interesting pharmacological effects due to their anticancer and antibacterial properties. Evidence suggests that certain types of flavonoids might have an important relevance on aging and brain pathology, as mediators in interactions between neurons and glial cells, among others. According to Nones et al., hesperidin, quercetin, and rutin (Figure 7) were used in the treatment on murine cerebral cortex astrocytes and neural progenitors. The results of these experiments showed that hesperidin-treated astrocyte (H-CM) yielded an increment in the number of neural progenitors and postmitotic neurons, and shining a "light" on the treatment of neurodegenerative diseases (Nones, Spohr, & Gomes, 2012).

Due to the interesting spectrum of biological properties that flavonoids and their derivatives can have in biological processes, they can be used in the treatment of chronic and infectious diseases, and also neurological dysfuctions. In this regard, the flavonoids more prone to be used are those that show selectivity and low cytotoxicity in *in vivo* assays. Our aim is to present the first "light" regarding the medical use that can be given to this type of compounds. Thus, we can extend the above-mentioned biological applications to nanotechnology, where some of these active flavonoids might be used in nanocapsule systems, whose effect would be to decrease the quantity and concentration of the polyphenol, making it extendable in time (drug delivery system) on the patient. Finally, the use of flavonoids as possible experimental drugs gives us the opportunity in decreasing the side effects of many commercial drugs and lowering the high economic costs associated with medical treatments.

3.1.1 | Isoflavonoids

Isoflavonoids have shown different biological properties including antifungal and antimicrobial activities as phytoalexins, anti-inflammatory activity by blocking some of the substances involved in inflammatory

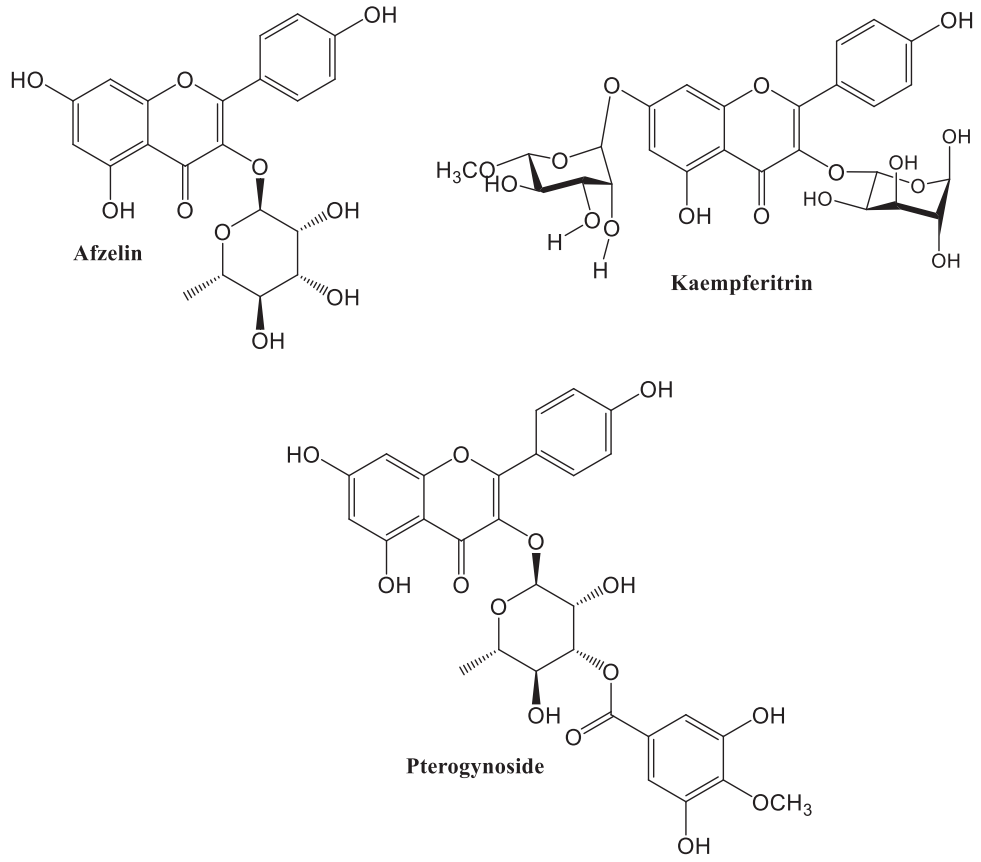


FIGURE 6 Chemical structures of afzelin, kaempferitrin, and pterogynoside

processes of the organism, insecticidal activity and used in fishing, and antioxidant activity directed against free oxygen radicals.

Only in recent years, in-depth studies have allowed us to discover other still unknown potentials of isoflavonoids. In this way, an intense estrogenic activity has been found; in fact, isoflavonoids represent the best-known class of phytoestrogens.

Phytoestrogens

In recent years, the interest in phytoestrogens has grown considerably. Epidemiological observations conducted since the 1950s, and more recently confirmed and further validated, have revealed that Asian women who make extensive use of soy foods (which is one of the main foods containing these substances) present, compared to women in Western countries, a lower incidence of breast cancer, cardiovascular disease, menopausal symptoms, and osteoporotic fractures. Even in men who make extensive use of food based on phytoestrogens, the incidence of prostate cancer has been reduced.

Therefore, the diet was evaluated above all based on the phytoestrogen content. However, we must also consider other factors such as lifestyle, sociocultural and morphological differences that distinguish the Asian population from the Western one.

Phytoestrogens structurally and functionally mimic mammalian endogenous estrogens showing powerful human health benefits; in fact, they play an important role in the prevention of cancer, cardiovascular diseases, symptoms of menopause, and osteoporosis (Adlercreutz, 2002).

Estrogens influence the growth and functioning of the reproductive systems, both male and female, the preservation of the skeleton and the good functioning of the central nervous system (CNS). They also show cardioprotective effects and prevent the onset of colon cancer and aging skin (Gruber, Tschugguel, Schneeberger, & Huber, 2002).

Phytoestrogens are functionally considered as substances that promote estrogenic activity in mammals and are structurally similar to endogenous estrogen 17β estradiol (E2). Other endogenous mammalian estrogens are estriol and estrone, which exhibit less estrogenic activity than E2 (Gruber et al., 2002).

Phytoestrogens were classified according to their chemical structure: steroidal estrogens found in a few plants, and the most ubiquitous phenolic estrogens, isoflavones, coumestans, and lignans. Other classes of phytoestrogens are anthraquinones, chalcones, flavones, prenylflavonoids,

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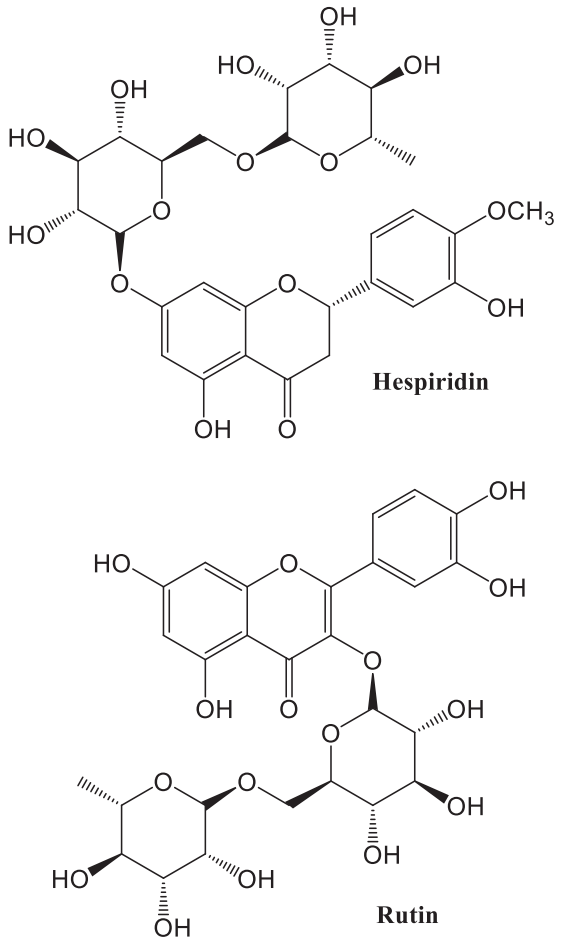

FIGURE 7 Chemical structures of hespiridin and rutin

and saponins (Siddique, Barbhuiya, Sinha, & Jayaprakash, 2019).

The isoflavones that showed the most estrogenic activity are daidzein (4′,7-dihydroxyisoflavone), genistein (4′,5,7-trihydroxyisoflavone), and glyciteine (4′,7-dihydroxy-6-methoxyisoflavone) originally isolated from *Glicyne max* and formononetine (7-hydroxy-4′-methoxyisoflavone) and biochanin A (5.7-dioxoxy-4′-methoxyisoflavone) isolated from *T. subterraneum*.

The estrogenic activity of isoflavonoids may be due to their ability to act as agonists, mimicking endogenous estrogens producing estrogenic effects, but also as antagonists by blocking or altering estrogen receptors (ER) by preventing estrogen activity. The antiestrogenic activity would also take place due to interference with the endogenous estrogen metabolism.

Phytoestrogens can bind to two types of ER: (1) ER, which was cloned in 1986, and (2) ER cloned in rats (Kuiper, Enmark, Pelto-Huikko, Nilsson, & Gustafsson, 1996) and in humans (Mosselman, Polman, & Dijkema, 1996). The two receptors differ in tissue distribution and affinity to ligands. ER has a very high binding affinity with phytoestrogens and in the human organism it is distributed in the ovary, in the spleen, in the testicles, and in the thymus (Mosselman et al., 1996). Phytoestrogens show a low binding affinity compared to E2 and some have higher affinity for ER than for ER, which determines different actions (Kuiper et al., 1996). A few years later, researchers identified a third ER in different tissues of the crab *Micropogonias undulates* (Hawkins et al., 2000). Steric and hydrophobic properties are important characteristics that allow chemical compounds to bind to ER as well as the hydrogen bond between the ER binding site and the phenolic hydroxyl group.

Isoflavonoids consist of a planar cyclic system, which includes a *p*-hydroxy-substituted aromatic ring, which is located at 12 Å from a second hydroxyl group on the plane.

Other features for ER-binding affinity are the degree and size of alkyl group branching, its location on the phenolic ring, and the electronic density on ring A.

Both genomic and nongenomic mechanisms have been proposed to explain the effects of phytoestrogens on human health. Phytoestrogens are capable of interacting with enzymes and receptors and due to their stable structure and low molecular weight, they can cross cell membranes (Adlercreutz, 2002).

Some genomic mechanisms of action concern estrogenic and antiestrogenic effects on ER, while other effects may not regard a direct interaction with ER. Nongenomic effects not related with ER include the inhibition of tyrosine kinase activity and DNA topoisomerase, induction of tumor cell differentiation, suppression of angiogenesis, and antioxidant effects (Barton, 2012). Furthermore, these substances influence the biosynthesis and metabolism of steroids and fatty acids and the intracellular and transmembrane transfer of hormones to the membrane and nuclear receptors. Phytoestrogens inhibit the enzymes necessary for the conversion of hormones that reduces tumors by lowering the activity of sexual hormones in target organs (Adlercreutz, 2002). Phytoestrogens are capable of inducing estrus in mammals due to be estrogen-like substances (Barton, 2012).

(i) Several recent studies have discussed the potential effects of phytoestrogens in the treatment of breast, endometrial, prostatic, and colorectal cancer, and of liver disorders (Molina, Bustamante, Bhoola, Figueroa, & Ehrenfeld, 2018).

Antitumor activity

Mammary tumor. In Western countries breast cancer is the most common pathology in women. Its incidence was very high in American women compared to Asian women before the introduction of Western nutrition into Asian

culture. The diet in these areas was deficient in fats and red meat but rich in fish (a source of vitamin D) and soy. A diet rich in estrogens is a protective agent against breast cancer, although obvious contradictions remain (Adlercreutz, 2002). Several studies have shown that overexposure of cells to estrogens alters the normal balance of growth. In fact, elevated estrogen levels are often associated with increased cell proliferation (Hilakivi-Clarke, De Assis, & Warri, 2013).

Several mechanisms have been suggested regarding the action of phytoestrogens on breast tissue. Several ER isoforms play an important role with a consequent reduction of estrogenic effects (Adlercreutz, 2002). There are other proposed mechanisms including alteration of growth factor activity and binding proteins, inhibition of angiogenesis, inhibition of tyrosine kinase and other protein kinases, inhibition of different enzymes such as 3-β-hydroxysteroid dehydrogenase, 17-β-hydroxysteroid dehydrogenase type 1, 5-α-reductase, phenol-sulphatase, topoisomerase I and II, and aromatase (Adlercreutz, 2002). Genistein and other soy isoflavones can also cause apoptosis in tumor cells both *in vivo* and *in vitro* (Adlercreutz, 2002).

Prostate cancer. Mortality from prostate cancer is very high in the Western world compared to Asian countries. Adlercreutz *et al*. recently studied the effects of genistein and its metabolites on cultured tumor prostate human cells (LNCaP, DU-145, and PC-3 cell lines) (Adlercreutz, 2002). The best activity among the tested isoflavones was shown by the 4′-methyl quol.

The actions observed in the prostate are consequent to the formation of the phytoestrogene-ER complex; the prostate contains both ERα and ERβ concentrated in different areas. Other mechanisms may be due to antiandrogenic effects, inhibition of 5-α-reductase activity, 17-β-hydroxysteroid dehydrogenase and aromatase, DNA topoisomerase II, tyrosine kinase, and antioxidant activity (Morrissey & Watson, 2003).

Several epidemiological studies have suggested a beneficial use of phytoestrogens in the reduction of prostate cancer. The results showed little protective effects on prostate cancer with greater consumption of phytoestrogens (Dobbs et al., 2018).

Some studies have also indicated the vitamin D system as protective in the onset of prostate cancer. In places of high exposure to sun the incidence of prostate cancer appears to be reduced since the synthesis of vitamin D in the skin depends on UV light. Farhan, Wähälä, Adlercreutz, and Cross (2002) conducted studies on a possible interaction of genistein with the vitamin D system. They reported that genistein is a potent inhibitor of CYP24, which proposes a new mechanism of action of isoflavones for the prevention of prostate cancer.

Cardiovascular diseases

They represent the main cause of death in industrialized countries. In menopausal women the risk of a cardiac ischemic event is higher and is due to low estrogen levels (Sathyapalan et al., 2018). Vascular reactivity, cell proliferation, and thrombosis are factors that influence the onset of cardiovascular disease and on which phytoestrogens have shown beneficial effects. The mechanisms of action involved are reduction of the plasma concentration of lipids, reduction of the formation of thrombus caused by a wall action (antiplatelet activity), improvement of arterial system compliance, and antioxidant activity (Sathyapalan et al., 2018). Several mechanisms of action are reported to explain the hypocholesterolemic effects of phytoestrogens and it concerns increased bile acid secretion, which help the removal of LDL cholesterol; interference with hepatic metabolism with greater removal of LDL cholesterol from hepatocytes; increased thyroid activity (Lissin, & Cooke, 2000).

Symptoms of menopause

Studies conducted in the early nineties have shown that in Japan, China, and other Eastern countries menopausal women have a very low incidence of symptoms typical of this condition such as hot flashes, genital dryness, wrinkles, hair fragility. This peculiarity has been attributed to the high consumption of foods containing phytoestrogens, in particular soy, by these populations.

Isoflavones can significantly reduce the menopausal-related disorders, so much so that they can be a valid alternative to hormone replacement therapy that involves a series of side effects such as swelling, behavioral disorders, increased risk of cancer.

The mechanism of action by which they act is not clear yet. Target tissues, the binding affinity with ER and the concentration of endogenous estrogens are all factors that influence the activity of phytoestrogens.

Other nonreceptorial mechanisms may also explain the biological effects of phytoestrogens on menopausal symptoms such as antioxidant activity, blocking of enzymes involved in estrogen biosynthesis, inhibition of protein kinase activity, and inhibition of 5-α-reductase and aromatase (Chen, Lin, & Liu, 2015).

Antioxidant activity

Because of their polyphenolic structures, isoflavonoids can donate hydrogen atoms to the harmful free radicals of oxygen and form less reactive phenolic radicals. The same structures give the isoflavonoids also the ability to chelate metal ions, mainly iron and copper,

capable of generating radical species for catalysis (Fenton reaction). In different studies, genistein, daidzein, and their metabolites have shown that the ability of these compounds to block free radicals only partially explains their antioxidant activity. An interesting observation of these studies has been that the genistein and daidzein metabolites have an antioxidant activity comparable or superior to their original compounds. Equol and its 4-hydroxy- and 5-hydroxy-derivatives showed potent antioxidant activity, which suggests that the absence of the 2.3 double bond and the 4-oxo group in the nucleus of the isoflavonoids increases the antioxidant activity (Pathak et al., 2018). Also, the extract of the root of *Glycyrrhiza glabra* has exhibited antioxidant activity. The flavonoid compounds with this activity are the isoflavans glabrene, glabridin, hispaglabridin A and B, 4′-O-methylglabridin, and the isoflavone formononetin.

3.2 | Lignans and flavonolignans

Soybeans, flaxseed, sunflower seeds, peanuts, grain cereals, vegetables including carrots, asparagus, and broccoli, and fruits such as plums and pears are sources of the major precursors of lignoid compounds. One of the most important functions of lignanoids is their role as phytoestrogens. Due to their hormone-regulating potential, they are beneficial for the treatment of menopausal symptoms, polycystic ovary syndrome, sex organ cancer, and osteoporosis. Phytoestrogen intake via vegetable diet has a relationship with lowering the risk of breast, colon, and prostate cancer. For instance, enterodiol and enterolactone show growth inhibitory activity against colon and ovarian tumor cells and are found to be mediated through their antiestrogenic action. The anticancer mechanism of lignoids is attributed to their antioxidant and regulating action on the key control points of the cell cycle. Furthermore, they possess antioxidant, anti-inflammatory, antimicrobial, enzyme inhibitory activities (i.e., aromatase, 5-α-reductase, 17P-hydroxysteroid dehydrogenase); they display modulatory effects on cardiovascular and immune systems as well as on liver functions and blood lipid profile (reduce low-density lipoprotein [LDL] cholesterol and increase high-density lipoprotein [HDL] cholesterol) (Liu et al., 2017).

Podophyllin, the resin of *Podophyllum*, exhibits antitumoral activity by providing antimitotic action. Etoposide and teniposide, semisynthetic derivatives used in clinical therapy, exert topoisomerase II inhibitory activity by inducing double stranded breaking of DNA molecules. It was reported that when taken at the early promotion stage of tumor genesis, secoisolariciresinol diglycoside possesses antitumor activity. This compound suppresses pulmonary metastasis of melanoma cells and inhibits metastatic tumor growth in the lungs. Other lignoids including phyllanthostatin A, megaphone acetate, dysodanthin A, dysodanthin B, schiarisanrin C, syringaresinol, brevitaxin, asarinin, xanthoxylol, deoxypodorhizone, nemerosin, morelensin, (−)-hinokinin, honokiol, machilin A, matairesinol, arctigenin, (−)-yatein, dihydroguaiaretic acid, and podophyllotoxins were found to be cytotoxic against skin, lung, and prostate cancer cells as well as lymphocytic leukemia and colon carcinoma. Heterolignanolides, obovatinal, perseal A and perseal B, heteroaromatic analogues of lignans, and formyl neolignans showed moderate antineoplastic effects against the tumor cell lines P-388 (Atta-Ur-Rahman, 2002; Watson & Preedy, 2008)

Dihydrodiisoeugenoland 5′-methoxydehydrodiisoeugenol exhibited antibacterial activity against the cariogenic bacterium *Streptococcus mutans*. Magnolol and isomagnolol were reported to be active against *S. cerevisiae, S. aureus, Mycobacterium smegmatis*, and *Trichophyton mentagrophytes*. Podophyllin was reported to possess antiviral activitiy against venereal warts caused by a papilloma virus via inhibition of topoisomerase, integrase, and reverse transcriptase as well as tubulin binding (Charlton, 1998). Schisantherin-D, schisandrin-C, kadsuranin, gomisin-G, anolignan A, anolignan B, phyllamycin B, phyllamycin E, retrojusticidin B, justicidins A and B, diphyllin, diphyllin apioside, diphyllin apioside-5-acetate, asarinin, xanthoxylol, rhinacanthin E, and rhinacanthin F exhibited good antiviral activity. More specifically, topoisomerase inhibitory effect for rabdosiin; suppression capacity of proviral DNA integration for (−)-arctigenin and (−)-trachelogenin; inhibitory activity of HIV replication for interiotherin A and schisantherin D were described. Aryltetralin-type lignans including 4′-(9-demethyldehydropodophyllotoxin) and picropodophyllone displayed good antifungal effect against *Allescheria boydii, Curvularia lunata, Drechslerarostrata, Epidermophyton fuccosum, Microsporum canis, Nigrospora oryzae*, and *Pleurotusostreatus*. Oleiferin-B, oleiferin-G, oleiferin-F, verrucosin, and 3,4,3′,4′-tetramethoxylignan-7-ol exhibited antifungal effect against *Cladosporium sphaerospermum* and *C. cladosporoides*. (+)-Nyasol exerted antiprotozoal activity against *Leishmania major* promastigotes. (+)-medioresinol, (+)-pinoresinoland (−)-lirioresinol B showed antileishmanial effect against *Leishmania amazonensis* amastigotes; veraguensin and grandisin demonstrated trypanosomicidal effect against *Trypanosoma cruzi* trypomastigotes; anolignan B and termilignan were active against the chloroquine-susceptible strain of *Plasmodium falciparum* (Barker, 2019). In terms of insecticide activity, sesamin, asarinin, savinin, and hinokinin improved the effects of

insecticides. β-peltatin-A methyl ether was active against housefly larvae. (+)-Haedoxan A and (+)-haedoxan D exerted insecticidal effect against *Musca domestica*. Conocarpan, eupomatenoid-5, and eupomatenoid-6 displayed insecticidal effect against mosquito larvae. Neolignans including magnolol, 4-methoxyhonokiol, and 4,4′-diallyl-2,3′-dihydroxybiphenyl ether were found to possess bactericidal and fungicidal potential and were toxic against brine shrimp and mosquito larvae (Rios, Giner, & Prieto, 2002; Saleem, Ja Kim, Ali, & Lee, 2005; Teponno, Kusari, & Spiteller, 2016).

Alcohol and CCl_4-induced liver damage could be prevented by lignoids due to their modulatory effect on blood parameters including aspartate aminotransferase and alanine aminotransferase, and on the concentrations of total cholesterol, triglycerides, and total bilirubin. Hepatoprotective activities of silymonin, silandrin, silybin, silydianin, silychristin, and 3-deoxysilychristin were reported against CCl_4- and galactosamine-induced heatotoxicity. Sesamin and episesamin inhibited lymphatic cholesterol absorption, enhanced fecal excretion, and notably inhibited cholesterol accumulation in liver. Histological assessment revealed that sesamin shows a remarkable inhibitory action against fat droplet accumulation and vacuolar degeneration as well as increased exogenous free fatty acid metabolism in liver (Saleem et al., 2005, articles therein). Similarly, in an *in vivo* study, sesamin and episesamin increased HDL and decreased serum VLDL concentration in normocholesterolemic rats, while only episesamin normalized serum lipoprotein levels in hypercholesterolemic rats. Secoisolariciresinol diglycoside decreased hypercholesterolemic atherosclerosis through decreasing serum LDL cholesterol and lipid peroxidation products as well as enhancing HDL cholesterol and inducing antioxidant mechanisms. Antioxidant potentials of sesamol, sesamolinol, sesaminol and pinoresinol, dihydroguaiaretic acid, guayacasin and isopregnomisin, gomisin N, cinnamophilin, kadsurin, kadsurenone, burchellin, magnolol, honokiol, enterolactone, prestegane B, 2,3-dibenzylbutane-l,4-diol, guayacasin, dihydroguaiaretic acid, schisanhenol, schizandrin, wuweizisu B, gomisin J syringaresinol and medioresinol were previously described. Wuweizisu C and schisantherin D were active in the CCl_4 test while deoxygomisin A, gomisin A, gomisin C, gomisin N, wuweizisu C, and schisantherin D were active in the galactosamine assay. After partial hepatectomy, liver regeneration was stimulated by gomisin A via ornithine decarboxylase (ODC) activity induction. Gomisin A also protected the liver from acetaminophen injury by inhibiting lipid peroxidation. In the rat liver homogenate, heteroclitin F and heteroclitin G inhibited Fe^{2+} ascorbic acid, CCl_4, NADPH, and ADP-NADPH-induced lipid peroxidation. (+)-Sesamin, (+)-sesaminol, (+)-episesamin, (−)-asarinin, and (−)-epiasarinin were reported to possess Δ^5-desaturase inhibitory effect in polyunsaturated fatty acid biosynthesis (Rios et al., 2002, articles therein; Saleem et al., 2005, 2005, articles therein; Teponno et al., 2016, articles therein).

Sesamin, neojusticin B, ephedradine B, danshensuan B, magnolol, (±)-pinoresinol diglucoside, and pinoresinol monoglucoside were revealed to possess *in vivo* hypotensive effect. KCl-induced rabbit aorta contraction was inhibited by graminone B without affecting NA-induced contractions. On the other hand, 2,3-dibenzylbutane-l,4-diol inhibited NA-induced contractions in rat aorta by enhancing cGMP levels. Moreover, pinoresinol, (+)-pinoresinol-β-D-glucoside, (−)-matairesinol, and arctigenin exerted high inhibitory activity against phosphodiesterase (PDE). Arctigenin, matairesinol, trachelogenin, nortrachelogenin, hypophyllanthin and lirioden-drin, fargesone A, B, and C, denudatin B, pinoresinol dimethyl ether, lirioresinol-B dimethyl ether, magnolin, and fargesin showed notable antagonistic activity on calcium channels. Lignan enriched traditional Chinese formulation, namely, *Sheng-Mai-San*, was found to be effective in the treatment of coronary disease in isoproterenol-induced myocardial injury and ischemia-reperfusion injury models via its antioxidant activity. Kadsurenone, honokiol, magnolol, (−)-denudatin B, cinnamophilin, and gomisin M showed an inhibitory effect on platelet activating factor (PAF) binding and platelet aggregation induced by PAF. Magnone A, magnone B, puberulin A, puberulin C, bistetrahydrofuran, and butanolide-type lignoids, inhibited PAF receptor binding; (+)-pinoresinol dimethyl ether, (+)-acetoxypinoresinol, dimethyl ether, (+)-isogmelinol, phillygenin, (+)-epipinoresinol dimethyl ether, fargesin, isomagnolin, arctigenin and arctigenin methyl ether, epiyangambin, (+)-yangambin, piperbetol, methylpiperbetol, piperol A and piperol B inhibited PAF-induced platelet aggregation. Taiwanin E, taiwanin E methyl ether, neojusticin A and justicidin B inhibited platelet AA-induced aggregation (Rios et al., 2002, articles therein; Prakash, & Gupta, 2011).

Neolignans, magnoshinin, and magnosalin inhibited the granuloma tissue formation while they had no effect on blood vessel permeability. Diphyllin acetyl apioside possessed strong activity against acute TPA-induced ear edema. Dibenzocyclooctadiene lignans were assessed in the same assay and gomisin A, gomisin J, and wuweizisu C inhibited the edema. Gomisin A and justicidin E were reported to inhibit LTB4 production. Cinnamophilin was found to be a selective thromboxane A2 (TXA2) receptor antagonist in human platelets, rat aorta, and guinea-pig trachea with voltage-dependent Ca^{2+} channel blocking activities. This compound also inhibited AA, collagen, and U-46619-induced human platelet-rich plasma

aggregation dose dependently. Lignans inhibited 5-LOX and COX, among them, (±)-pinoresinol was the most active as 5-LOX inhibitor; (−)-prenylpiperitol was the most active as COX inhibitor. Other 5-LOX inhibitor active compounds were (+)-epiashantin, (±)-syringaresinol, (−)-prenylpiperitol, and (−)-prenylpluvia-tilol. Eudesmin, magnolin, and lirioresinol-B dimethylether demonstrated suppressing activities on the production of TNF-α in lipopolysaccharide (LPS)-stimulated murine macrophage cell lines. (+)-Pinoresinol exhibited analgesic activity on writhing symptoms in mice, which was dose dependent. Cinnamophilin showed *in vivo* beneficial effect against reperfusion injury of the ischaemic skeletal muscle. By inducing fibroblasts and collagen production, dihydrobenzofuran lignan, 3′,4-0-dimethylcedrusin, was found to facilitate healing of wounds in *in vivo* models. Americanol A, isoamericanol A, and americanin A increased choline acetyltransferase effect in a cultured neuronal cell system. Schisandrin showed strong inhibitory action on the CNS. In *in vivo* models, magnolol and honokiol provided antidepressant and muscle relaxation activity via central action (Rios et al., 2002), articles therein; Saleem et al., 2005, articles therein; Szopa, Dziurka, Warzecha, Kubica, & Klimek-Szczykutowicz, 2018).

In summary, lignoids have been reported as the active principles of antimicrobial, anticarcinogenic, hepatoprotective, and phytoestrogenic medicinal plants.

3.3 | Stilbenoids

Chemically, stilbenoids are a group of phenolic compounds sharing a backbone stilbene structure, which can be found in various plant species. Stilbenoids play the role of phytoalexins in plants and owing to their chemical diversity have diverse biological activities. Among them, resveratrol and combretastatins are popular due to their chemopreventive effects against cancer. Owing to the structural similarity to diethylstilbestrol, resveratrol has estrogenic receptor affinity and modulates the balance of estrogenic functions (Aggarwal et al., 2004).

Stilbenoids have antioxidant potential due to their polyphenol functions in their structures. Some of their beneficial actions, including among others, hepatoprotective, cardioprotective, anti-inflammatory, and anticarcinogenicones are related to their antioxidant effects. Resveratrol and analogs, marchantin H and marchantinquinone, parthenostilbenins, gneafricanins, bisisorhapontigenins, vitisinols, (+)-e-viniferin, (−)-viniferal, ampelopsin C, (+)-vitisin C, sophorastilbene A, paeoninol, longusone A, flavonostilbenes, and gnetoflavanols exhibited either inhibitory activity on bleaching alkoxyl radicals and lipid peroxidation or scavenging free radicals (Akinwumi & Bordun, 2018, articles therein).

Several studies have pointed out antifungal, antibacterial, and antiviral activities of stilbenoids especially for resveratrol and glepidotin D (HIV-1 and HSV-1), scirpusin A and scirpusin B (against HIV-luIB); pinosylvin (fungal shoot blight and canker pathogen of conifers *Sphaeropsis sapinea)*, isorhapontin (against *Trichoderma viride)*, stemofurans (against *Alternaria citri, Fusarium avenaceum, Pyricularia grisea Botrytis cinerea*, and *Cladosporium herbarum*); bisbibenzyls, bazzanin B, and isoplagiochin D (against *Pyricularia oryzae*), marchantin C, neomarchantin A, neomarchantin B, GBB A, and GBB B (against *T. mentagrophytes* and *B. subtilis*); plagiochin E, neomarchantin A, and 13,13′-O-isoproylidenericcardin D, dehydroeffusol and juncusol (against *Candida albicans*); andalasin A (against *Bipolaris australiensis*); combretastatins A-4 (816), A-5, and A-6 (against *Neisseria gonorrhoeue*); combretastatin B5 (against *S. aureus*); (E)-resveratrol 3-(6″-galloyl)-O-β-D glucopyranoside, gnetin E, parthenocissin A, e-viniferin, a-viniferin, hemsleyanols B and D, vaticanol B and davidiol A, hopeaphenol A, vaticaphenol A (against oxacillin/methicillin-resistant *Staphylococcus aureus* [MRSA]); prenylated stilbenes (against *P. falciparum* and *B. subtilis*) (Akinwumi, & Bordun, 2018, articles therein).

The anticancer potential of the stilbenoids are due to their inductive effect on cytotoxicity and apoptosis, PDE inhibition, DNA cleavage activity, as well as antiproliferative effects. Stilbenes suppress procarcinogen metabolic activation and prevent the carcinogenesis initiation by inhibiting cytochrome P450 (CYP) isoforms in cell lines. Especially resveratrol and its analogs were found to be effective in carcinogenesis prevention. Resveratrol increases the elimination of carcinogens from the body and suppresses actions of transcription and growth factors. Resveratrol exhibits cytotoxicity against various cancer types, that is, breast, liver, pancreatic, prostate, and colorectal cancer (Carter, D'Orazio, & Pearson, 2014). Owing to its lipophilic character, pterostilbene displayed higher inhibitory activity on human colon cancer cells. Piceatannol, an analog of resveratrol, exerted antiproliferative effect on AH109A hepatoma cells through induction of apoptosis and antioxidation. Gnetol was demonstrated to have anticancer activity via histone deacetylases and cytochrome enzymes (CYP2C9 and CYP3A4) inhibition. Anticancer potential of schweinfurthins A, B, D, and synthetic analogs were screened against 60-cell line and showed strong cytotoxicity. Lakoochin A and B, racemosol, and demethylracemosol displayed cytotoxicicty against breast cancer cell lines; racemosol and demethylracemosol were also active against KB cell lines. Riccardin C, another stilbenoid compound, displayed cytotoxic activity against KB

cell lines. A selective DNA polymerase p inhibitory action was provided by pusilatins B and C. Eoumarin hybrid demonstrated cytotoxicity against a LuI cell line. Vaticanol C provided significant cytotoxicity in a variety of cell lines and inhibited cell growth in colon cancer cell lines via apoptosis induction. Besides vaticanol C, vaticanol B, isovaticanol C, upunaphenol A, and upunaphenol G inhibited HL60 cell growth by inducing apoptosis. Combretastatins, paritcularly combretastatin A-4, were investigated for their chemopreventive activity and were revealed as a tubulin inhibitor. 3,3′-dihydroxy-2′,6′-bis(phydroxybenzyl)-5-methoxybibenzyl and 3′,5-dihydroxy-2-(phydroxybenzyl)-3-methoxybibenzyl were shown to inhibit the tubulin polymerization. Nepalensinols showed potent inhibitory effects on topoisomerase II, which were stronger than the anticancer drugs etoposide or daunorubicin. Dihydrophenanthrenes showed significant cytotoxic activity against several cell lines including A549, SK-OV-3, and HL-60 (San Cheang et al., 2015, articles therein; Tringali, 2012, articles therein).

Resveratrol, piceatannol, aiphanol, isorhapontigenin, and racemosol have been demonstrated as potent anti-inflammatory agents as they inhibit both clooxygenase-1 (COX-I) and clooxygenase-2 (COX-2). Stemofurans B, D, G, and J and stilbostemin G exerted anti-inflammatory activity by inhibiting leukotriene formation. Gnetupendin B inhibited the production of prostaglandin E2 (PGE2) in LPS-stimulated mouse peritoneal macrophages. Bisbibenzyls displayed anti-inflammatory effect via LPS-induced nitric oxide synthase (NOS) inhibition in RAW 264.7 macrophages. (+)-a-Viniferin showed a prostaglandin H2 synthaseinhibitory potential higher than that of resveratrol. Furthermore, it displayed remarkable anti-inflammatory effect on carrageenin-induced paw edema in mice by suppressing the release of prostanoids and NO. Amurensin F (+)-hopeaphenol, isohopeaphenol, vitisin A, (+)-vitisifuran A, heyneanol A, stemanthrene A (356), and stemanthrene D exerted inhibition of leukotriene B4 (LTB4) biosynthesis. Gnetumontanin B, bisisorhapontigenin B, gnetupendin C, gnetupendin D, cis-E-Viniferin and 2b,14b-dehydro-bisresveratrol showed inhibitory activity on TNF-α. Artocarpol A inhibited superoxide formation in phorbol 12-myristate 13-acetate stimulated rat neutrophils and TNF-αformation in LPS-stimulated RAW 264.7 cells (Dvorakova & Landa, 2017).

Resveratrol was found to protect neurons from Parkinsonism by hydroxyl radical scavenging action and also protected against LPS-induced dopaminergic neurodegeneration through the inhibition of microglial activation and NFkB signaling. Resveratrol was reported to be effective in the treatment of Alzheimer's disease by protecting against neuronal death and reducing amyloid plaques through the promotion of proteasome-dependent degradation of amyloid-beta in the brain. Pterostilbene demonstrated neuroprotective effect by inhibiting ROS generation against high glucose-induced injury in neuroblastoma cells. Pterostilbene was also reported to improve cholinergic transmission. The tetramer neohopeaphenol A, (+)-a-viniferin, and kobophenol A are regarded as new AChE inhibitors for Alzheimer's disease, exhibiting their action by acetylcholinesterase (AChE) inhibition (Tringali, 2012, articles therein; Niesen, Hessler, & Seeram, 2013, articles therein).

In preclinical and clinical studies, resveratrol inhibited platelet aggregation, which was attributed to cyclooxygenase (COX)-1 suppression, MAPK pathway inhibition, and nitric oxide/cGMP pathway activation. Pterostilbene also possessed an inhibitory effect on platelet aggregation similar to resveratrol (Messina et al., 2015). Ampelopsin C, (−)-viniferal, miyabenol A and (+)vitisin C, marchantinquinone, and gnetol showed antiplatelet activity (Xiao et al., 2008, articles therein). By increasing glucose uptake and translocation of GLUT 4 to the caveolar membrane of diabetic myocardium, resveratrol prevented hyperglycemia in diabetic animals. It improved glucose tolerance and decreased the advanced glycated end-products receptor expression in the liver and kidney of diabetic rats. Resveratrol inhibited nitrogen species, superoxide anion, hydroxyl radical, hydrogen peroxide, and malondialdehyde production, and increased SOD, catalase, and glutathione peroxidase levels in diabetic animals. Resveratrol also suppressed proinflammatory signaling, nuclear factor kB (NFkB), decreased inflammatory cytokines production, and increased insulin sensitivity and glucose tolerance. Pterostilbene prevented pancreatic beta cells from oxidative stress and improved glycemic control in insulin-resistant obese rats. Desoxyrhapontigenin and rhapontigenin displayed α-glucosidase inhibition and inhibited postprandial hyperglycemia. Pterostilbene decreased the blood glucose level of hyperglycemic rats (Xiao et al., 2008, articles therein; Gómez-Zorita et al., 2015; Soufi, Mohammad-Nejad, & Ahmadieh, 2012; Tastekin et al., 2018).

Other biological activities were also reported for silbenoids. (+)-e-Viniferin was found to be a hepatoprotective agent against CCl_4-induced hepatic injury in mice. Aloifol II, 1,5,7-trimethoxyphenanthrene-2,6-diol, ephemeranthoquinone, gigantol, lusianthridin, batatasin III, coelonin, 3,7dihydroxy-2,4-dimethoxyphenanthrene, 3,7-dihydroxy-2,4,8-trimethoxyphenanthrene, fimbriol-A, nudol, gymnopusin, and erianthridin exhibited smooth muscle relaxant effects. *Trans* and *cis*-dehydrodimers of resveratrol, Melapinols A and B, vaticanol A and ampelopsin C, chlorophorin showed 5-α-reductase inhibitory activities.Oxyresveratrol, piceatannol, gnetol,

mulberroside F, 4-prenyloxyresveratrol, artocarbene, artogomezianol, pterostilbene, and andalasin possessed potent tyrosinase inhibitory activity (Xiao et al., 2008, articles therein; Akinwumi, Bordun, & Anderson, 2018, articles therein).

Resveratrol reduced arterial compliance and systolic blood pressure in spontaneously hypertensive rats. In a randomized double-blinded placebo-controlled trial, pterostilbene decreased systolic and diastolic blood pressure at higher doses. The studies demonstrated the protective effects of resveratrol and pterostilbene on myocardial ischemia-reperfusion injury through anti-inflammatory and antioxidant fuctions and modulatory actions on vascular function and gene expressions related to lipogenesis and lipolysis, lowering the effects on lipid accumulation, levels of plasma LPS, LDL-cholesterol, and lipid peroxidation (Akinwumi et al., 2018; Chang et al., 2011; Riche et al., 2014; Rimando, Nagmani, Feller, & Yokoyama, 2005, articles therein).

In summary, stilbenoids show several biological actions including anti-inflammatory, anticarcinogenic, cardio- and neuro-protective, and antidiabetic activities by regulating various signaling pathways. Even though resveratrol remains to be the compound responsible for most activities, further studies are warranted to reveal and clarify the beneficial effects of stilbenoids.

3.4 | Tannins (HT, CT, phlorotannins, flavono-ellagitannins)

Tannins are the natural-based polyphenolic compounds that are capable of converting animal skin into leather. Fruits including apples, pears, peaches, plums, cranberries, strawberries, grapes, and beverages like tea and wines were reported to contain tannins. Morever, *Acer ginnala, Quercus infectora*, *Caesalpinia spinosa, Casesalpinia brevifolia, Hamamelis virginiana, Terminalia chebula*, *Schinopsis* species, and *Eucalyptus sieberiana, Coriaria*, *Agarobilla*, and *Schinopsis* species are the sources of tannins.

The molecular weight of water-soluble tannins is between 500 and 3,000 D, containing hydroxyl and other functional groups, which enable them to form cross-linkages with macromolecules such as proteins and gelatin. Due to the formation of complexes with these macromolecules, the nutritional value and bioavailability of foods (particularly iron and vitamin B12) were reported to be reduced when taken with tannin-like compounds, especially CT. In animal studies, tannins were reported to be responsible for the decline of feed intake, protein absorption, digestion, and other enzymatic activities. If consumed in large amounts, it can cause gastrointestinal tract mucosa and liver damage, alteration of protein and essential amino acid excretion, and even toxicity and fatal poisoning. Therefore, it is not recommended to consume high tannin-containing foods in large amounts (Delimont, Haub, & Lindshield, 2017).

In some previous animal studies, tannins were reported to be both mutagens and carcinogens. However, there are some paradoxal outcomes rearding this issue. Although, the Occupational Safety and Health Administration listed tannins in Category I as tentative carcinogens, there is a general consideration that tannins may act as cocarcinogens in inducing carcinogenesis in the presence of other carcinogens (Chung et al., 1998, articles therein).

A remarkable negative correlation between tea consumption and stomach cancer incidence was reported in a study conducted in 20 countries. Japanese people, frequently consuming green tea, were shown to have lower gastric cancer risk. Green tea polyphenol fraction was demonstrated to inhibit 12-*0*-tetradecanoylphorbol-13-acetate (TPA)-induced tumor induction, as well as UV light–induced tumorigenesis in mouse skin. The extracts of green tea, also inhibited B[*a*]P,7,12-dimethylbenz[*a*]anthrance and *N*-methyl-*N* nitrosourea, TPA, teleocidin, okadaic acid, 7,12-dimethylbenz[a]anthracene (DMBA) a,nd (+)-7β-8α-dihydroxy-9α,10α-epoxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene (BPDE-2)-induced tumorigenicity when topically applied to mouse skin (Chung et al., 1998, articles therein).

Green tea infusion significantly suppressed *N*-nitrosodiethylamine (NDEA)-induced tumorigenesis and decaffeinated green tea and black tea extracts also inhibited 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK)-induced lung tumorigenesis in A/J mice. Besides these cancers, green tea extracts were also reported to inhibit different types of tumors such as mammary, liver, pancreas, esophageal, forestomach, duodenum, small intestine, and colon. These effects were mainly attributed to the major polyphenolic compound epigallocatechin gallate (EGCG). In *in vitro* and *in vivo* studies, ellagic acid was also reported to inhibit tongue, esophageal, lung, liver, and colon cancers by inhibiting the procarcinogen metabolism, protecting DNA and scavenging ROS and adduct formation of carcinogens. Furthermore, gallic acid and tannic acid were also shown to be active in inhibiting the formation of tumor and mutagens. HT oligomers including agrimoniin, oenothein B, and coriariin A displayed antitumor effects against sarcoma by promoting cytotoxic effect and activating the natural killer (NK) cells and cytostatic macrophages. The anticarcinogenic and antimutagenic activities of tannin-type compounds could be obtained owing to their antioxidative and cell protective features by inhibiting the generation of superoxide

radicals (Chung et al., 1998, articles therein; Macáková et al., 2014, articles therein).

The antimicrobial activity of tannins has been reported in several studies. Antifungal effects of tannins against *C. albicans, Fomes annosus*, *Merulius lacrymans* and *Penicillium* species, *Crinipellis perniciosa*, *B. cinerea*, *Coriolus versicolor, Poria monticola* 198, and *Aspergillus niger, Chaetomium cupreum, Colletotrichum graminicola, Coniophoraolivacea*, *Gloeophyllum trabeum*, *Trameteshirsuta*, and *T. viride* have been reported. Antibacterial activity of tannin-type compounds has been described against *S. aureus, S. epidermis, Streptococcus pnumonia, S. mutans, S. sobrinus, S. pyogenes, S. lactis, S. faecalis, Shigella dysenteriae, S. flexneri, Salmonella senftenber*g, *S. enteritidis, S. paratyphi, B. cereus*, *B. anthracis, B. subtilis*, *B. stearothermophilus*, *Clostridium botulinum, Desufomaculum nigrificans, Enterobacter aerogenes, E. cloacae, Pseudomonas maltophila, Pseudomonas solanaceacrum, Proteus vulgaris, P. mirabilis, Photobacterium phosphoreum, Sporo cytophaga* sp., *Polyangium* sp. *Desulfovibrio* sp., *Nitrosomonas* sp., *Vibrio parahaemolyticus, V. fluvialis*, *V. metschnikovii*, *Clostrisium perfringens*, *Plesiomonas shigelloides*, *Aeromonas sobria, E. coli, Klebsiella pneumoniae*, *Galliandra portoricensis, E. coli, K. pneumoniae, Listeria monocytogenes, Yersinia enterocolitica, Agmenellum quadrupliacatum, Flexibacter columnaris*. Tannins have also been reported to be effective against herpes viruses, influenza viruses, reoviruses, coxsackievirus, echovirus, and polioviruse. Recent studies have shown that galloyl and hexahydroxydiphenoyl esters possess anti-HIV activity (Chung et al., 1998, articles therein).

Many studies have been conducted to reveal the biological activities of ellagic acid such as blood clotting, and blood pressure reducing effects. Tannic acid was reported to have inhibitory effect on hyaluronidase enzyme. Serum and liver lipid-lowering activity of tannic acid was demonstrated in a high-fat diet fed to genetically hypercholesterolemic (RICO) and normocholesterolemic (RAIF) male rats. It was reported that tannic acid (25 or 30 g/kg) affected in a dose-dependent manner the immune function of growing chickens when added to their diets. Agrimoniin was isolated as an immunomodulatory substance from *Agrimonia pilosa* Ledeb displaying its efficacy by enhancing NK cell activity. Tannic acid was reported to have antiallergenic activity against allergic diseases including asthma, allergic rhinitis, and hypersensitive pneumonitis. Tannins, especially tannic acid, were also used as a topical agent for treating burn wounds. Clinical studies have revealed that either a single application of tannic acid or its combination with other drugs helps to reduce pain and provides rapid hemodynamic stabilization (Chung et al., 1998).

Briefly, tannins in optimal doses have promising effects for human health modulating the metabolic enzymes, immune system, and other functions. Due to the possible risk of antinutritional effects, cancer induction, and other adverse reactions, high amounts of tannins are not recommended.

3.5 | Curcuminoids

Curcuminoids are the main polyphenols present in turmeric rhizomes (*Curcuma longa* Linn), a member of the Zingiberaceae family. The bioactive effects of turmeric derives mainly from curcuminoids: curcumin (diferuloylmethane) and two associated compounds demethoxy curcumin and bisdemethoxycurcumin, although there are also studies on synthetic derivatives of curcumin (Paramasivam, Poi, & Banerjee, 2009). The main biological activities of curcuminoids include antioxidant, anti-inflammatory, antiproliferative and antitumor, neuroprotective, and wound healing capacities. However, many other biological activities have also been indicated such as antimicrobial, antivenom, cardio-protective ones, or protective against gastrointestinal and metabolic diseases (Salehi et al., 2019).

The pharmacological activity of curcumin and curcuminoids is largely related to their ability to neutralize oxidants. Curcumin has a high hydrophobicity, which means that its antioxidant activity will mainly occur in lipophilic structures (Sökmen, 2016). The capacity of curcumin to eliminate free radicals comes from the presence of OH group in the phenolic ring or from the CH_2 group of the β-diketone moiety. The anti-inflammatory effects of curcumin have been widely investigated by many authors in cell cultures and animal models but also in clinical trials using rheumatoid arthritis and osteoarthritis as main target diseases (Khan, El-Khatib, & Rainsford, 2012). Curcumin has been found to inhibit the synthesis and release of prostaglandins and proinflammatory cytokines (Anthwal et al., 2014). The antiproliferative and antitumor effects of curcuminoid and synthetic derivatives have been widely investigated in cell culture and animal models, and there is a remarkable amount of clinical trials on this issue (Salehi et al., 2019). The mechanisms by which curcuminoids carry out their antitumor actions are multifactorial depending on the study model and include as targets the pathway of NFκB, p53, $p21^{Cip1}$, Bcl-2, and the activation of apoptotic cell death and induction of autophagy (Hong, Ping, Dong, Jing, & Liang, 2015). For example, the effect of curcuminoids on breast cancer is now widely studied. The antitumor effect against breast cancer is, in part, related to targeting the oestrogen receptor (Hallman et al., 2017). Also, significant antimetastasis effects have been

evidenced by the downregulation of extracellular matrix degradation enzymes urokinase plasminogen activator, metalloproteinases (Einbond, Wu, & Kashiwazaki, 2012). Regarding clinical trials, some studies have shown symptomatic relief or a reduction of tumor markers in various types of cancer, including multiple myeloma, brain, breast, lung, prostate, colorectal cancer (Salehi et al., 2019). Neurodegenerative disorders such as Alzheimer's or Parkinson diseases are complex and multifactorial and include within their pathophysiological alterations inflammation and an excessive production of reactive species in various signalling pathways (Ataie, Sabetkasaei, Haghparast, Moghaddam, & Kazeminejad, 2010). Generally, regarding the different neurological diseases, curcuminoids have been shown to suppress the elevation of the intracellular levels of Ca^{2+}, reduce nitric oxide production and reactive oxygen and nitrogen species (RNOS), and reduce proinflammatory mediators (de Alcântara et al., 2016).

More specifically, they can act on specific pathways depending on the pathology studied. In Alzheimer's disease curcumin is able to interfere with Aβ fibrils and aggregates exerting and depolymerizing activity and to inhibit the phosphorylation of tau protein (Orteca et al., 2018). Another remarkable action of curcuminoids is their ability to protect the skin against various aggressions. Numerous studies have observed beneficial effects of these compounds against psoriasis, pruritis, vitiligo, radiation-induced dermatitis, skin regeneration, and wound healing in a process mainly mediated by scavenging free radicals and reducing inflammation via the inhibition of NFκB (Ryan et al., 2013).

3.6 | Coumarins

The great structural diversity of coumarins as well as the type of substituents and the pattern of substituents present in the coumarin scaffold allow this type of compound to present a wide variety of pharmacological actions. Coumarin derivatives are widely used in pharmaceutical companies and also have several biological and pharmacological effects including antimicrobial, antiviral, antioxidant, antiulcerogenic, anti-inflammatory, antinociceptive, antispasmodic, anticancer, anticoagulant, vasodilator, and anxiolytic ones. Hepatotoxicity, nausea, carcinogenicity, and diarrhea have been reported as side effects of coumarin derivatives (Venugopala, Rashmi, & Odhav, 2013).

The physicochemical characteristics of the oxaheterocyclic ring of coumarins facilitate the binding to numerous protein targets as it is an aromatic and lipophilic ring (Stefanachi et al., 2018). These properties favor the ability of coumarins to interact with their biological targets, mainly at lipophilic binding sites. In addition, the presence of a lactone group gives the molecule the capability of establishing strong polar bindings. The lactone ring can also be opened by the action of esterases generating new compounds with further biological activities. In addition to the antioxidant and anti-inflammatory activities that characterize the majority of polyphenols, the pharmacological activities of coumarins also include antimicrobial, anti-tuberculosis, anti-HIV, anticancer, anticonvulsant, monoamine oxidase inhibitor, lipid-lowering, and anticoagulant activities (Zhu & Jiang, 2018).

Regarding the antioxidant effects, the presence of hydroxyl substituents on the structure of coumarins makes them effective scavengers of ROS and reactive nitrogen species (RNS) (Kostova et al., 2011). It seems that the most effective antioxidant form is that which has two hydroxyl groups in ring A in ortho position because the catechol moiety can undergo bielectronic oxidation originating a very stable quinone (Filipský et al., 2015). In addition to direct scavenging activity, coumarins are also able to act as strong metal chelators and to directly inhibit ROS- and RNS-producing enzymes such as myeloperoxidase, xanthine oxidase, or lipoxygenase (Filipský et al., 2015). In relation to inflammation, coumarins exhibit a remarkable anti-inflammatory capacity derived from the inhibition of the production of several cytokines such as IL-6, IL1β, and TNFα, and increased production of the anti-inflammatory cytokine IL-10 (Kirsch, Abdelwahab, & Chaimbault, 2016). Coumarins have also been reported to inhibit the expression of proinflammatory enzymes such as COX-2, iNOS in a process associated to the inhibition of the NFκB and MAPK pathways (Jin et al., 2018). Probably, the most representative biological activity of coumarins is the one related to their anticoagulant action (Daly, 2013). Coumarins such as warfarin (a vitamin K antagonist), phenprocoumon, and acenocoumarol have been used as antithrombotic agents and are among the most widely prescribed drugs (Zaragozá et al., 2016). Many studies have reported the chemical synthesis of 4-hydroxycoumarin derivatives because of their high anticoagulant activity (Lei et al., 2015). Coumarins have been also been found to exert antibacterial, antifungal, and antiviral activities. Several structural characteristics have been described that increase the antimicrobial activities of coumarins, such as the presence of free hydrolyl groups, long chain hydrocarbon substitutions, various osthole derivatives, and some linear and angular pyranocumarins (Venugopala et al., 2013). One interesting effect of coumarins is their potential for the treatment of *Mycobacterium tuberculosis* since there is a growing increase of multidrug-resistant strains (Keri, Sasidhar, Nagaraja, & Santos, 2015). Another aspect of interest of coumarins is the ability of some of them such as tetracyclic pyranocoumarins to inhibit HIV replication (Olomola, Klein, Mautsa, Sayed, & Kaye, 2013). The

number of coumarin compounds with anticarcinogenic effects increases progressively, with great diversity of cell targets reducing the proliferation or inducing apoptosis in tumor cells (Lu et al., 2016). However, as for most polyphenols, their effects have been developed mainly in cell cultures or animal models, which make their potential transfer to human beings difficult. Moreover, some coumarins have demonstrated anticonvulsive effects, which may be a therapeutic support in the treatment of neurological disorders such as bipolar disorder or epilepsy (Karataş et al., 2016). Some coumarin derivatives have also been reported to exert antidepressant activities acting preferentially as monoamine oxidase inhibitors. Finally, coumarins and several derivatives have been found to act as lipid-lowering agents with therapeutic potential in dyslipidaemias (Tejada et al., 2017).

4 | POSSIBLE INTERACTIONS

Polyphenols are largely used for their health promoting effects. For this reason, their bioavailability has been intensively examined. Several studies have also evaluated the possible interactions of these secondary metabolites with other foods constituents, particularly carbohydrates, proteins, and lipids (Kardum, & Glibetic, 2018).

Polyphenols interact with several carbohydrates generally by forming hydrogen bonds. Covalent bonds are also described. The possibility of improving the uptake of polyphenols by carbohydrates has been reported. The stability of proanthocyanidin dimers and trimers under digestion conditions, their bioavailability, and metabolism have been investigated (Serra et al., 2010). Serra et al. (2010) showed that proanthocyanidin dimers and trimers are absorbable with a maximum concentration in plasma 1 hr after ingestion and that the absorption of these compounds is blocked by the concurrent presence of foods that are rich in carbohydrates. A previous study also demonstrated that the consumption of carbohydrates considerably increased flavanol (epicatechin and catechin) uptake (Schramm et al., 2003). Probably, polyphenol bioavailability is subject to the release of these phytochemicals from the complex with carbohydrates, which, in turn, are influenced by the structure of polyphenols and the complexity of polyphenol–carbohydrate interactions. Positive effects of polyphenol–carbohydrate interactions in the large intestine have been described. In fact, polyphenols could be released from the complex by the action of microorganisms and enzymes in the colon, exerting their positive effects (Tuohy, Conterno, Gesperotti, & Viola, 2012).

Some studies have demonstrated that dietary fibers may act as carriers of polyphenols to the colon where they can exert antimicrobial effects against pathogenic microorganisms and increase the growth of beneficial microorganisms (Saura-Calixto, 2011). Microbial degradation can be affected by the chemistry of both phenols and foods.

The polyphenol–protein interactions represent a continuous research topic. These interactions are principally noncovalent interactions (hydrogen, ionic bonding, and hydrophobic) (Nagy et al., 2012). Covalent interaction has also been shown between proteins and quinones formed by oxidation of flavonoids. The most studied binding targets are plasma proteins, particularly albumin. However, besides proteins present in the plasma, interactions between phenols and proteins of foods have been reported. Interactions between polyphenols and proteins are influenced by both molecular weight and chemical structure. Generally, it was found that bigger compounds bind proteins more strongly. These interactions have shown important effects. Some studies have reported a decrease of the availability of tryptophan, cysteine, and lysine, after the interaction of polyphenols with proteins (Rohn, Petzke, Rawel, & Kroll, 2006). In addition, protein structure may be altered. Modification of biological properties of proteins in the gastrointestinal tract have also been described (Aguié-Béghin, Sausse, Meudec, Cheynier, & Douillard, 2008). Polyphenols could bind to some enzymes and could modify their activity. An example is the interaction of CT with α-amylase (Gonçalves, Mateus, & de Freitas, 2011). Some works have analyzed how the bioavailability of polyphenols may be influenced by polyphenol–protein interactions. Van het Hof, Kivits, Weststrate, and Tijburg (1998) demonstrated that milk added to tea did not modify catechin bioavailability. Minimal effects on cocoa catechin absorption by proteins from meals was also reported by Schramm et al. (2003). Conversely, in another study milk produced negative effects in humans on coffee polyphenol bioavailability (Duarte & Farah, 2011). Different results have been obtained more recently (Ribnicky et al., 2014). In this work, authors examined the bioavailability of polyphenols, by using a polyphenol-rich extract obtained from *Artemisia dracunculus* and a complex of polyphenols with soy proteins. Data from this work showed better bioavailability and bioaccessibility of polyphenols sorbed to soy proteins. Studies have suggested that the biological properties of polyphenols (mainly their antioxidant activity) and polyphenol bioavailability could be affected by polyphenol–protein interactions. Interactions between polyphenols and milk proteins have been reported. These interactions can delay the appearance of polyphenols in the blood (Dupas, Marsset-Baglieri, Ordonaud, Ducept, & Maillard, 2006). On the other hand, proteins could protect phenols in the gastrointestinal tract from oxidation reactions. Besides food proteins, polyphenols can interact with enzymes. These interactions could have several important consequences. Polyphenol-rich extracts from

several plant foods have been identified as very interesting inhibitors of α-glucosidase and α-amylase activities (Tundis et al., 2016).

Unlike interactions with carbohydrates and proteins, several studies demonstrated that the interactions between polyphenols and lipids slightly influence the absorption of polyphenols.

Like antioxidants, polyphenols could serve to stabilize some foods such as plant oils toward oxidation. In the past years, there has been a growing interest in using some polyphenols as food additives. Moreover, lipids present in foods could increase the absorption of polyphenols. Guo et al. (2013) demonstrated, for example, that dietary lipids improved the bioavailability of quercetin by increasing its absorption, likely by improving its micellarization at the small intestine. Previously, Azuma, Ippoushi, Ito, and Higashio (2002) described an enhanced absorption of quercetin by concomitant administration of an emulsifier and some lipids such as lecithin. In another work, the coadministration of green tea as a phospholipid complex increased the absorption of catechin (Pietta et al., 1998). Several studies investigated not only the role of lipid concentrations on the bioavailability of polyphenols but also the effects due to various types of lipids. Indeed, the chain length of fatty acids has been shown to affect the micellarization of polyphenols during digestion. It has been determined that bioavailability of phenolic compounds was enhanced by 38% and 12% after intake along with medium-chain fatty acid and long-chain fatty acid diets, respectively, compared to standard diets (Lesser, Cermak, & Wolffram, 2006). In addition, the degree of saturation can affect the bioavailability of the polyphenols.

Goltz, Campbell, Chitchumroonchokchai, Failla, and Ferruzzi (2012) demonstrated that unsaturated fat promoted carotenoid absorption better than saturated fat. It has been suggested that dietary fat can probably promote the solubility of polyphenols (Lesser, Cermak, & Wolffram, 2004; Mateo Anson, van den Berg, Havenaar, Bast, & Haenen, 2009).

As described in several studies, lipids affect the kinetics of absorption of some polyphenols. Mullen, Edwards, Serafini, and Crozier (2008) investigated the bioavailability of the anthocyanin pelargonidin-3-*O*-glucoside by using a cream with *Fragaria* × *ananassa* (strawberry). The obtained results showed that after ingestion of strawberries pelargonidin-3-*O*-glucoside is converted mainly to pelargonidin-*O*-glucuronide, which is the dominant anthocyanin in plasma and urine. The influence of the cream resulted in a delayed absorption of pelargonidin-*O*-glucuronide from the small intestine.

Taking into account all the above-mentioned results, it is evident that polyphenol interactions with carbohydrates, lipids, and proteins, and the consequent effects should be further investigated.

5 | CURRENT AND POTENTIAL INDUSTRIAL APPLICATIONS

Besides the direct use of polyphenolics as health improvement agents and/or against disease conditions in medicine or nutraceuticals, they have been widely used in various other industrial applications (Figure 8).

The functional activity of natural compounds depends on their chemical properties and structural features and with the use of advanced analytical techniques for the extraction, identification, and purification of these compounds; it could be possible to optimize their activity. The main action of polyphenols is to chelate free radicals and thus, they are widely used as an antioxidant and antimicrobial component in multi-industries such as, agro-food, nutraceutical, cosmetic, and meat and food packaging industry (Table 2). In agro-food industry polyphenols have been used as additives for different purposes. For instance, among its additive roles it has been used to prevent microbial activity of food products (Cetin-Karaca & Newman, 2015), and prevent rancidity by limiting enzymatic activity and oxidation of food products. Also, it has been used in food products to enhance their organoleptic properties. Anthocyanins, for instance, which is one of the flavonoid class of compounds responsible for the bright red, blue, and purple color of fruits and vegetables, are used as natural pigments in food products. In cereal products, such as cookies and bread, anthcyanins from grapes are used to enhance the acceptability and durability of the product (Acun & Gul, 2014). Overall there has been an increase in the use of anthocyanins as a color pigment in various food products such as dairy, cereals, beverages, juices, and ice creams.

In the meat industry polyphenols are added to prevent lipid oxidation, microbial growth, and thus increase product shelf-life. For instance, pomegranate peel extract was found effective in delaying lipid oxidation and protein oxidation of beef meatballs (Turgut & Soyer, 2016). Also, the extract of kordoi (*Averrhoa carambola*) increased shelf-life when added to pork nuggets (Thomas, Jebin, & Saha, 2016). Moreover, olive leaf extract when applied to pork prevents protein and lipid oxidation (Botsoglou, Govaris, & Ambrosiadis, 2012).

As the antioxidant activity of polyphenolics has been proven effective against a number of disease conditions, industry has taken advantage of this to formulate a number of effective nutraceutical products, such as dietary supplements and functional foods (Gollucke, Peres, Odair,

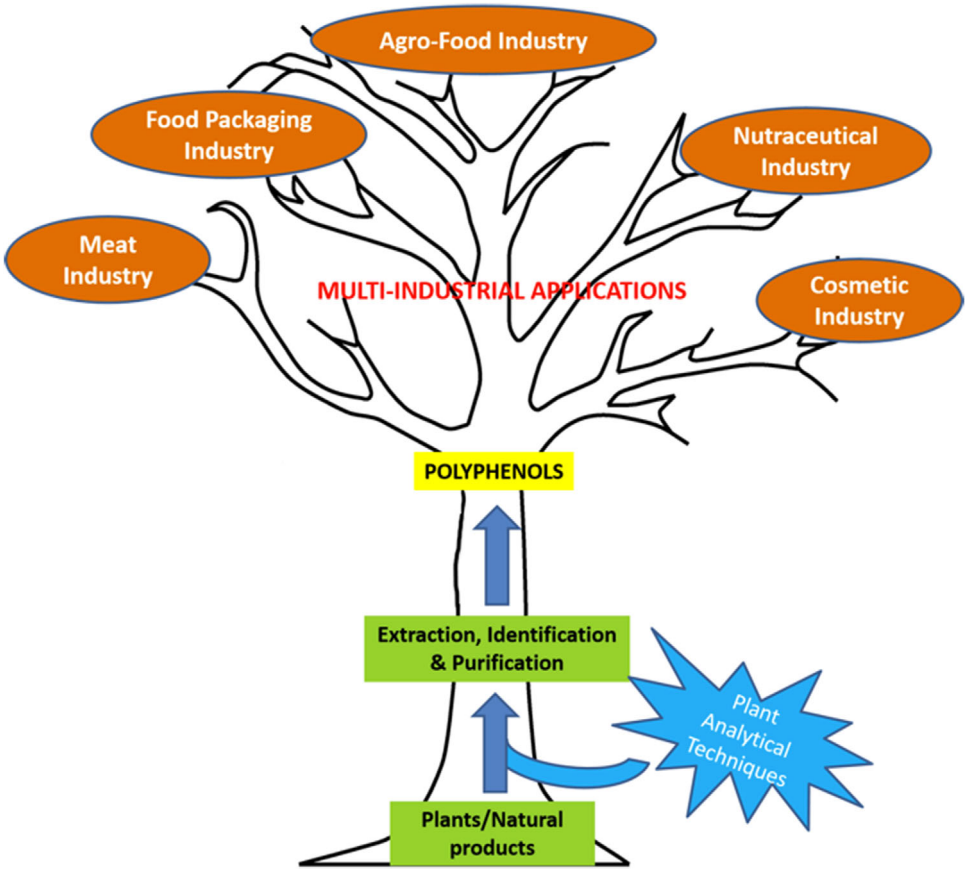

FIGURE 8 Industrial applications of polyphenols

TABLE 2 Multi-industrial uses of polyphenolics and their applicability

Industry type	Industrial uses	Applicability
Agro-food	Antimicrobial agent	• Extend the shelf-life of food products
	Antioxidant agent	• Reduce rancidity • Prevent free radical reactions, induced by light, metal, and oxygen • Reduce enzymatic activity such as lipoxygenase
	Food additives	• Provide good smell, taste, and color
Nutraceuticals	Dietary supplements	• Prevent from chronic degenerative disease including metabolic, cardiovascular, tumor
Meat	Antioxidant, antimicrobial	• Prevent lipid oxidation and enzymatic activity • Increase shelf-life • Prevent microbial activity • Enhance color and odor
Food packaging	Antioxidant and antimicrobial activity	• Extend the shelf-life of product
Cosmetic	Antiaging, antioxidant, and antimicrobial	• Prevent skin aging and protect skin • Protect skin from harmful UV radiations

& Ribeiro, 2013). For instance, polyphenolics from plant sources have been widely tested both *in vitro* and *in vivo* experiments and have shown strong antioxidant activity (Belwal, Giri, Bhatt, Rawal, & Pande, 2017), which help prevent degenerative diseases including metabolic, cardiovascular, and tumoral ones (Kim et al., 2017). Among other industrial uses of polyphenols, the cosmetic industry has used polyphenols due to their antiaging, UV-protectant, anti-inflammatory, and antimicrobial activities (Joshi & Pawar, 2015). In cosmetic products polyphenolics are mainly used as antioxidants and antiaging agents due to their free radical scavenging activity, which prevents oxidative stress on skin cells. Moreover, UV protective cream and/or lotions also contain polyphenolics, which prevent the skin from harmful UV radiations and thus delay aging (Joshi, & Pawar, 2015). The antimicrobial activity of polyphenolics has also been utilized in cosmetic products, which prevents microbial growth especially fungus on to the skin, thereby improving skin function.

In recent years, growth of the food packaging industry increased by incorporating active packaging, which not only prolongs shelf-life of products but also effectively enhances their physicochemical properties. Polyphenolic compounds are used in active packaging due to their antimicrobial and antioxidant activity. Polyphenolics from rosemary (Abdollahi & Rezaei, 2012), tea (Wang, Dong, Men, & Tong, 2013), oregano, and garlic (Seydim & Sarikus, 2006) are used in food packaging for their antioxidant and antimicrobial activity.

The multi-industrial uses of polyphenolics require an optimum extraction, identification, and purification from the plant matrix. Moreover, green analytical techniques are a prerequisite for obtaining polyphenolic compounds for their safer and more effective uses in food products. A future need is to combine innovative and green analytical techniques for extracting polyphenolics given their wide industrial applications.

6 | CONCLUSIVE REMARKS AND FUTURE TRENDS

The great structural diversity of polyphenols allows to understand their wide biological properties. From these properties, antioxidant activity deserves special attention and allows to understand the effects of these compounds on different diseases, like oncological, cardiovascular, and neurodegenerative conditions, and conditions like menopause.

It is evident that polyphenols interact with carbohydrates, dietary fibers, lipids, and proteins and this should be better investigated because it greatly affects their availability. For instance, polyphenols interact with several carbohydrates, generally by forming hydrogen bonds, improving the uptake of polyphenols. In what concerns to dietary fibers, these may act as carriers of polyphenols to the colon where they can exert antimicrobial effects and increase the growth of beneficial microorganisms.

Polyphenols are used directly to improve human health, but they can also be used in other industrial applications such as agro-food and food industries to improve food shelf-life and quality. Moreover, polyphenols have also a wide range of applications in what concerns to the different types of cosmetics due to their antioxidant, antimicrobial, and antiaging properties.

Due to the increasing importance of polyphenols, it is essential that the critical review of the extraction procedures and analytical methods applied to polyphenols and their selection criteria over a wide range of factors. This will be the aim of the second part of this review on polyphenols.

AUTHOR CONTRIBUTIONS

Conceptualization of the review was carried out by A. Sanches Silva and S. M. Nabavi; writing of the original draft was performed by A. Sanches Silva, P. Reboredo-Rodríguez, I. Süntar, A. Sureda, T. Belwal, L. Rastrelli, M. R. Loizzo, R. Tundis, E. Sobarzo-Sanchez, T. Y. Forbes-Hernandez, M. Battino, R. Filosa, M. Daglia; revision and editing of the final version was carried out by A. Sanches Silva, P. Reboredo-Rodríguez, T. Y. Forbes-Hernandez, and M. Battino; supervision was performed by S. F. Nabavi, S. M. Nabavi, and A. Sanches Silva. All authors have read and agreed to the published version of the article.

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