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ORIGINAL PAPER

Cardioprotection by Phytochemicals via Antiplatelet Effects and Metabolism Modulations

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Abstract The multi-factorial aetiology is the characteristic element of cardiac disorders. Further scientific research had recognized for a long time that platelet function is related to the risk of developing atherosclerosis. Activated blood platelets play a central role in this chronic inflammatory condition as they contribute to plaque formation within blood vessels in the early stages of atherogenesis. The present review article summarizes the cardioprotective role played by Phytochemicals via antiplatelet effects. Also, various metabolic modifications have been included that have protective effect during cardiac pathology.

Keywords Cardioprotection · Phytochemical · Metabolism modulation · Curcumin · Resveratrol · Phenolics · Polyphenols · Antiplatelet effects

Introduction

The expression 'phenolic compounds' embraces a vast range of organic substances which are aromatic compounds with hydroxyl substituents. The parent compound is phenol but most are polyphenolic (characterised by the presence of more than one phenol unit per molecule). While a small number of phenolics occur in animals, most are of plant origin. Indeed, the presence of 'phenolic fraction' is a characteristic feature of all plant tissues. The biological properties of plant phenolics are many and varied, ranging from scents and pigments, poisons and feeding deterrents, allelopathic compounds, signalling molecules, structural components, and antifungal and antimicrobial agents. Polyphenols constitute one of the most ubiquitous groups of plant metabolites with more than 8000 phenolic structures currently known. The main source of polyphenols is dietary, since they are found in a wide array of phytochemicals bearing foods. For example, most legumes; fruits such as apples, blackberries, blueberries, cantaloupe, cherries, cranberries, grapes, pears, plums, raspberries and strawberries; and vegetables such as broccoli, cabbage, celery, onion and parsley and honey are rich in polyphenols. Phenolic compounds are also present in red wine, chocolate, green tea, olive oil, bee pollen and many grains. Forages such as crownvetch, lespedeza, lotus, sainfoin and trefoil are also reported to contain polyphenolic compounds.

Dietary polyphenols show a great diversity of structures ranging from simple molecules (monomers, oligomers) such as phenolic acids to polymerised compounds such as condensed tannins. Plant polyphenols are economically important as they make major contributions to the taste, flavour and colour of our food and drink. The flavour and taste of tea is related to the fact that the tea leaf contains up to 30 % of its dry weight as polyphenols. Likewise, the bitterness of beer is due to the content of the phloroglucinol derivative and humulone while the colour of red wine is imparted by anthocyanins such as the pigment malvin.

Recently interest in food phenolics has increased greatly, owing to their antioxidant capacity (free radical scavenging and metal chelating activities) and their possible beneficial implications in human health, such as in the treatment and prevention of cancer, cardiovascular disease, and other pathologies. In the last two decades, the interest in polyphenols has increased enormously and likewise the numbers of reports on the potential health benefits of polyphenols to prevent chronic diseases have increased. This review provides the available scientific data that

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justify importance of polyphenols in prevention of various pathologies that have an important public health burden like cardiovascular diseases (mainly coronary artery disease), cancer, osteoporesis and inflammatory reactions.

Plant polyphenolic Compounds are a Diverse Group with a Common Aromatic Ring Structure: Classification and Dietary Source

Plants produce a large range of phenolic compounds with diverse structures and properties that have several hydroxyl groups on aromatic rings (polyphenol structure) but also molecules with one phenol ring such as phenolic acids and phenolic alcohols. The simplest form is the phenol molecule itself and though the free phenol is never found in plants, so this structure can usually be recognised somewhere within a plant phenolic molecule. Most of the plant phenolics are frequently referred to as phenylpropanoids as they are synthesised from the products of the phenylpropanoid pathway. The basic structure of a phenylpropanoid is a phenyl ring with a three-carbon side chain attached (C_6–C_3; Fig. 1a).

In plants, phenolic compounds occur primarily in their mono-glycosylated form [1, 2]. Glucose is the predominant glycosyl moiety; however, arabinose, galactose, rhamnose and xylose are also common [3–5]. In addition to conjugation, the aromatic rings of phenolic compounds also contain varying degree of hydroxylations and methoxylations. This variation in the complexity of structure associated with conjugations, hydroxylations and methoxylations account for a wide range of naturally occurring phenolic compounds. About 8000 different plant phenolic have been identified to date and thus polyphenols are among the most widespread class of metabolites in nature and their distribution is almost ubiquitous.

Phenolic compounds can be divided into different classes depending on their basic carbon skeleton structure [2, 4] as shown in Table 1. However, the phenolic compounds can also be categorised by the number of phenolic rings and structural elements that link these rings [6] viz: [1] The phenolic acids with their subclass derived from hydroxybenzoic acids and hydroxycinnamic acid; [2] flavonoids; [3] stilbenes; [4] lignans and the polymeric lignins. Their chemical structure may range from quite simple compounds like phenol with a gram molecular weight of 94 g/mol, to highly polymerized compounds such as proanthocynadins, which range in gram molecular weight from 500 to greater than 10,000 g/mol [7].

The simple phenolics: The simple phenolics are a mixed group of phenolic compounds with three main groups viz: simple phenylpropanoids, coumarins and benzoic acid derivatives (Fig. 1a–c).

The simple phenylpropanoids consists of a basic phenylpropanoid structure, with a three-carbon side chain attached to a six-carbon phenyl ring. The phenylpropanoids are the central units with a linear side chain. The common example for simple phenylpropanoids include the hydroxycinnamic acids i.e. caffeic, ferulic and cinnamic acids. These compounds are rarely encountered in free form and are generally glycosylated derivatives of quinic, shikimic or tartaric acid [8], as hydroxyl acid esters with large phenolic compounds such as flavonoids or with structural components of the plants such as cellulose, linin and protein [9]. For example, caffeic acid and quinic acid combines to form a chlorogenic acid which is found in high concentrations in coffee and many fruits, mainly blueberries and kiwis. Firulic acid is the most abundant phenolic acid found in cereal grains and wheat grains (Table 2).

The coumarins also have the basic C_6–C_3 phenylpropanoid skeleton but with a cyclized side chain to form a ring. Examples of coumarins include coumarins, umbelliferone, esculetin and scopoletin. Coumarins are found in coconut oil, lavender, liquorice, Tonka beans (hence the vanilla scent), apricot, cherries, strawberries and cinnamon. However, its usage in human diet is restricted due to possible liver damage by its excessive intake and is therefore banned as a food additive in most countries.

A third group of simple phenolics is the benzoic acid derivatives (hydroxybenzoic acids) that have a C_6–C_1, rather than a C_6–C_3 structure. Variations in the hydroxybenzoic acids occur due to differing patterns of hydroxylation and methoxylation of their aromatic rings. The majority occurs as glycosides or esters linked with aliphatic organic acids such as maleic and tartaric acids [10], or large phenolic compounds such as flavonoids [11, 12]. Examples include vanillin and salicylic acid (Fig. 1c) as well as gallic acid and erusic acid that are components of the hydrolysable tannins. Hydroxybenzoic acid such as gallic, *p*-hydroxybenzoic and vanillic acid are present nearly in all plants [1, 13]; however, they are found in very few plants that are consumed by humans and thus are not of high nutritional interest. However, there exist few exceptions in plants wherein the content of benzoic acid derivatives are richly present such as red fruits i.e. blackberries, raspberries, strawberries and tea (a rich source of gallic acid).

The complex phenolics: The complex phenolics consist of polyphenolic structures which include flavonoids, stilbenes, lignins and tannins (Fig. 1d–f).

Flavanoids

The term flavonoid has been derived from the latin word flavus meaning yellow, as large number of flavonoids are yellow in colour. Flavanoids are the largest group of naturally occurring phenolic compounds with over 6000 known types and especially common in higher plant families viz: Leguminosae, Rutaceae, Primulaceae,

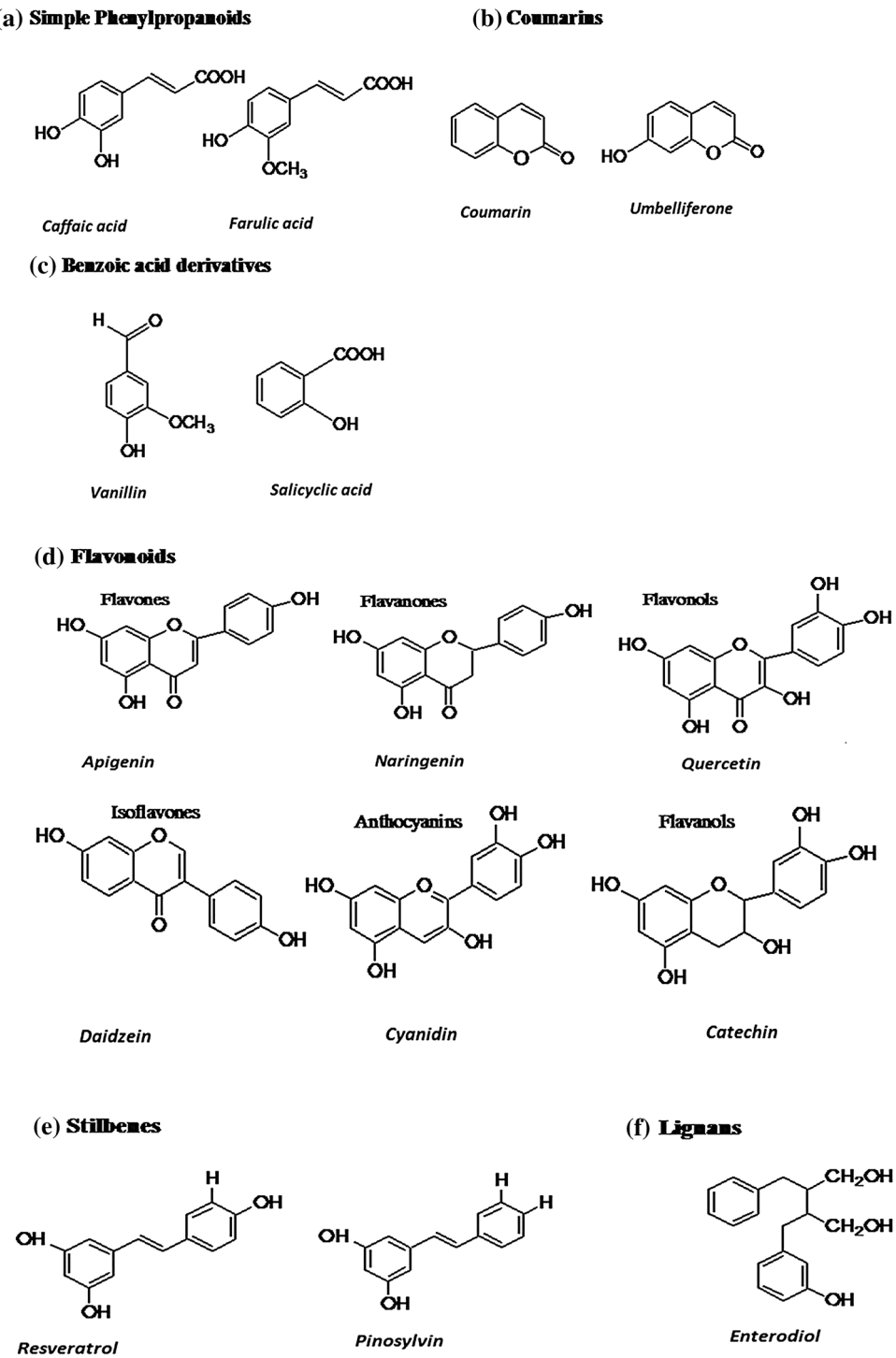

Fig. 1 Chemical structures of polyphenols

Polygonaceae, Salicaceae, Pinaceae, Rosaceae, Asteraceae, Lamiaceae, Bignoniaceae, Moraceae, Betulaceae, Rubiaceae and Myrtaceae. These compounds account for 60 % of the total dietary phenolic compounds [14–16].

Flavonoids occasionally occur in plants as aglycones though they most commonly occur as glycoside derivatives. Each hydroxyl group and certain carbons can be substituted with one or more of a range of different simple carbohydrates which, in turn, may be acylated with a variety of phenolic or aliphatic acids [15, 17]. Additional substituents on the flavonoid skeleton structure can include benzyl, innamyl, hydroxyl, isoprenyl and methoxyl [15]. Thus, the great diversity in the structure of flavanoids is because of the occurrence of numerous substitution patterns in which primary substituents can themselves be substituted by additional glycosylations or acylations.

Table 1 Basic carbon skeleton of phenolic compounds

Phenolic class	Carbon skeleton
Simple phenol	C_6
Hydroxybenzoic acids	C_6–C_1
Phenylacetic acids	C_6–C_2
Hydroxycinnamic acids, coumarins	C_6–C_3
Napthoquinones	C_6–C_4
Xanthones	C_6–CC_6
Stilbenes, anthroquinones	C_6–C_2–C_6
Flavonoids	C_6–C_3–C_6
Tannins	$(C_6–C_1)_n$, $(C_6–C_3–C_6)_n$
Bioflavonoids	$(C_6–C_3–C_6)_2$
Lignans	$(C_6–C_3)_2$
Lignins	$(C_6–C_3)_n$

There can be two stereoisomeric forms that can be possible for flavonoids that are unsaturated between C-2 and C-3, since C-2 is an asymmetric centre. Consequently, the B ring can be either in the (2*S*)- or (2*R*)-configuration. The majority of flavonoids that are isolated from plants have the (2*S*)-configuration because the enzymaticnreaction catalyzing the formation of these compounds is stereospecific [18].

All flavanoids have the same basic skeleton, consisting of two six-carbon rings (ring A and ring B) linked by a three-carbon bridge that usually forms a third ring (ring C, as shown for flavanone, Fig. 1d). The degree of oxidation of the central pyran (ring C) forms the basis of further classification of the flavonoids into various chemical groups. These groups include flavone, flavanones, flavonols, isoflavones, anthocyanidins and the flavanols which include catechins and proanthocynanidins (condensed tannins; Fig. 1g) and their structural differences are stated as follows:

i. Flavone: contains benzo-γ-pyrone ring with phenyl substitution at position 2 of the pyrone ring. Flavones consist chiefly of glycosides of luteolin and apigenin. Nearly 700 flavones [17] have been identified in plants with variation in acylation, glycosylation, hydroxylation, methylation and sulphation in the aromatic rings thus accounting for this large number [17]. Flavones are less common in plants as compared to other flanonoids but are prominent in citrus [19]. The important edible sources of flavones are the parsley and celery, though they are also present in hotpepper, oregano, rosemary and thyme. Also the skin of the fruits contains large quantities of polymethoxylated flavones (tangeretin, nobiletin and sinensetin).

ii. Flavanones: 2,3-dihydroderivative of flavone is called flavanone. Numerous structural variations of flavanones are found in plants due to acylation, glycosylation, hydroxylation, methylation and methoxylation of the A and B-rings of the carbon skeleton [18]. Glycosylation of flavanones typically occurs at the C-7 position (ring A). Flavanones are richly present in the solid parts of citrus fruit, particularly the albedo (the white spongy portion) and the membranes separating the segments, and thus the whole fruit may contain flavanone up to five times as much as a glass of juice.

iii. Flavonol: is three hydroxy derivative of flavone and represents the most ubiquitous flavonoids in food, with quercetin as the more representative compound. These compounds are present in glycosylated forms. The associated sugar moiety is very often glucose or rhamnose, but other sugars such as galactose, arabinose, xylose, glucuronic acid may also be involved. Since, their biosynthesis is stimulated by light, flavonols accumulate in the outer and aerial tissues (skin and leaves) of the plant. Marked differences in concentration exist between pieces of fruit on the same tree and even between different sides of a single piece of fruit, depending on exposure to sunlight [20]. The main sources of flavonols are onions, curly kale, leeks, broccoli, blueberries, tea and red wine.

iv. Isoflavones: contains benzo-γ-pyrone ring with phenyl substitution at position 3 of the pyrone ring. Isoflavones have structural similarities to oestrogens. Although they are not steroids, they have hydroxyl groups in positions 7 and 4 in a configuration analogous to that of the hydroxyls in the estradiol molecule. This confers pseudohormonal properties on them and can bind to oestrogen receptors, and they are consequently classified as phytoestrogens [2]. They contain three main molecules: genistein, daidzein, and glycitein, generally in a concentration ratio of 1:1:0.2. These isoflavones are found in four forms [1] aglycone [2] 7-*O*-glucoside [3] 6″-*O*-acetyl-7-*O*-glucoside and [4] 6″-*O*-malonyl-7-*O*-glucoside [21]. In contrast to most other flavonoids, isoflavonoids have a rather limited taxonomic distribution, mainly within the *Leguminosae*. Isoflavones are present almost exclusively in leguminous plants and thus the main source of it is soya and its processed products contain three main molecules i.e. genistein, daidzein and glycitein.

v. Anthocyanins: These occur primarily as glycosides of their respective aglycones form called anthocynadins with the sugar moiety mainly attached at the 3-position on the C-ring or at the 5, 7-position on the

Table 2 Polyphenols and its dietary sources

Class	Dietary polyphenol	Dietary source
Hydroxycinnamic acids	Chlorogenic acid,	Major: Blue berry, apple cider, kiwi, plum, cherries and coffee
	Caffeic acid	Other: pear, orange, lemon, peach, grapefruit, potato, spinach, lettuce, red wine and tea
	Ferulic acid	
	p-coumaric acid	
	Sinapic acid	
	Caftaric acid	
Hydroxybenzoic acids	Gallic acid	Major: red fruits (strawberry, raspberry and blackberries), black radish, onions and tea
	Ellagic acid	Other: grape juice, pomegranate juice, red wine and longan seed
	Corilagin	
Coumarins	Coumarin	Tonka beans, pulp of lime, celery, parsley and coriander leaves
	Furanocoumarins	
Flavones	Apigenin	Major: celery, fresh and dry parsley, skin of citrus fruits
	Luteolin	Other: olives, oregano, rosemary and thyme
	Tangeretin	
	Nobiletin	
	Sinensetin	
Flavanones	Naringenin	Major: orange juice, grape fruit, lemon and lemon juice
	Hesperetin	Other: tomatoes and pappermint
	Eriodictyol	
Flavonols	Quercitin	Major: apple, tea, beans, lentils, peppers, onions, broccoli and blueberries
	Myrecitin	Other: red wine, cocoa powder, turnip, endive, leek, dill weed, currants, buckwheat, kale, chives and dock leaves
	Fisetin	
	Kaempferol	
	Isohamnetin	
Isoflavones	Genistein	Major: soyabean, soya milk, soy flour, soy nuts, tofu yougurt and soya cheese
	Daidzein	Other: grape seed/skin
	Glycitein	
	Equol	
Anthocyanins	Cyanidin	Aubergine, blackberry, blackcurrant, blueberry, black grape, cherry, rhubarb, strawberry, red wine, plum and red cabbage
	Malvidin	
	Delphenidin	
	Pelargonidin	
	Peonidin	
	Petunidin	
Flavanols	Catechin	Major: green tea and chocolate
(Flavan-3-ols)	Epicatechin	Other: beans, apricot, grapes, peaches, cherry, blackberry apple, green tea, black tea, red wine, cider, resins, pear and nectarines
	Epicatechin 3-gallate	
	Morin	
	Epigallocatechin	
	Gallocatechin	
	Procyanidins	
	Prodelphinidins	

Table 2 continued

Class	Dietary polyphenol	Dietary source
Tannins	Catechin Polymers	Red wine, coffee, chocolate, tea, cocoa, grapes, pomegranate, apple juice, berries, nuts, cloves, cumin, thyme, cinnamon, longan, olive, plum and berries
	Epicatechin polymers	
	Ellagitannins	
	Proanthocyanadins	
	Tannic acids	
	Casuaricitin	
	Sanguin H6	
Stilbene	*Trans*-resveratrol	Grapes, red wine, peanuts, soy and itadori tea
	Cis-resveratrol	
Lignins	Secoisolariciresinol	Major: Flax seed and sesame seed
	Matairesinol	Other: pumpkin seeds, whole grains, cranberries, green and black tea, broccoli and soyabeans
	Pinoresinol	
	Lariciresinol	

A-ring. Anthocyanins exist as pigments dissolved in the vacuolar sap of the epidermal tissues of flowers and fruit, thus impart a pink, red, blue, or purple colour [22]. They exist in different chemical forms, both coloured and uncoloured, according to pH. They are highly unstable in the aglycone form (anthocyanidins), while they are in plants; however, they are resistant to light, pH, and oxidation conditions that are likely to degrade them. Degradation is prevented by glycosylation, generally with glucose at position 3, and esterification with various organic acids (citric and malic acids) and phenolic acids. Glycosylation provides stability to the anthocyanins and may also occur at other positions in addition to C-3, often at C-5 [22, 23]. The most common glycosyl group are monosaccharides, especially glucose, galactose, rhamnose and arabinose. Di- and trisaccharides formed by combinations of these four monosaccharides also occur [24]. The C-3 glycosylation is a prerequisite for further modifications, such as a second glycosylation, acylation, methylation and prenylation [23]. As a result of modifications to the basic structures of these pigments, more than 500 types of anthocyanins have been reported in plants [22]. In addition, anthocyanins are stabilized by the formation of complexes with other flavonoids (copigmentation). The most common acyl group associated with anthocyanins are the hydroxycinnamic acids, particularly caffeic, ferulic and *p*-coumaric acids, and the aliphatic dicarboxylate, malonic acid [17]. It is presumed that acylation with aromatic organic acids contribute to intra and/or intermolecular stacking for the stabilization of the pigment molecules [17]. Further, acylation increase water solubility and may serve as protection against enzyme-catalysed glycosidase degradation [23]. The human diet is widely composed of anthocyanins and are richly found in red wine, fruits (blackcurrants or blackberries, cherries and strawberries), certain variety of cereals and vegetables (cabbage, beans, onions and radish). Food contents are generally proportional to colour intensity and the levels of anthocyanins increase with fruit ripening. Anthocyanins are found mainly in the skin, except for certain types of red fruit, in which they also occur in the flesh (cherries and strawberries).

vi. Flavanols contain a saturated three-carbon chain with a hydroxyl group in the C3. The flavanols largely occur in the aglycone form, contrary to the fact that most flavonoids exist in plants as glycosides [25]. They exist in both the monomer and the polymer form (Catechins and proanthocynadins, respectively). Monomeric flavanols that are hydroxylated at position C-4 of ring C are known as flavan-4-ols while flavanols with an additional hydroxyl group at position C-3 of ring C are called flavan-3,4-diols, respectively. These compounds are also known as leucoanthocyanidins that are converted to anthocynadins by cleavage of the C-ring hydroxyl group upon heating with acid [26]. Catechins are found in many fruits such as apricots and cherry. Green tea, chocolates and red wine are by far the richest sources of catechins. Proanthocynadins, also known as condensed tannins, have a wide range of structures and molecular weights and thus it is very hard to value the proanthocyanidin content in food. However, they are as abundant in the form of dimmers and trimers of catechins as the

catechins themselves. Proanthocynadins are present in fruits (grapes, apples and berries), beverages (wine, cider, tea, beer and etc.) and chocolates.

vii. Other minor flavonoids: In addition to the aforementioned main subclasses of flavonoids, there exist three main subclasses of flavonods viz: chalcones, dihydrochalcones and aurones. The unique feature that distinguishes chalcones and dihydrochalcones from other flavonoids is the open chain three-carbon structure linking the A- and B-rings in place of a heterocyclic C-ring. The three-carbon linkage between the aromatic rings is unsaturated in chalcones, while it is saturated in dihydrochacones. Structurally, chalcones are among one of the most diverse groups of flavonoids and are found as monomers, dimmers, oligomers and conjugates of various types. Biosynthetically, these are the immediate precursors of all other classes of flavonoids.

The aurones are based on the 2-benzylidine-coumaranone or 2-benzylidin-3(2*H*)-benzofuranone structure [25]. These are not common in dietary plants although they have role in colouration. Aurones provide a strong yellow colour in variety of flowers and have been identified in bark from some ornamental trees such as Golden larch [27] and leaves from medicinal shribs [28].

Stilbenes

Stilbenes are structurally characterised by the presence of a 1,2-diphenylethylene nucleus with hydroxyls substituted on the aromatic rings and exist in the form of monomers or oligomers. Low quantities of stilbenes are present in the human diet and the main representative is resveratrol, that exists in both *cis* and *trans* isomeric forms, which is mostly glycosylated. However, the best known compound is trans-resveratrol, which possesses a trihydroxystilbene skeleton. More than 70 plant species are there that are abundant in resveratrol including grapes, peanuts and berries.

Lignans

Lignans are produced by oxidative dimerization of phenylpropane units. Although most of lignans are in free form; however, there also exist its glycosylated derivatives in minor forms. Lignans comprise a variety of compounds, both in food sources (secoisolariciresinol and matairesinol) and in the human body that metabolises the lignans to enterodiol and enterolactone by the action of intestinal microflora [29, 30]. Mammalian lignans enterolactone and enterodiol are considered to be products of colonic bacterial metabolism of the plent-derived precursors mateiresinol and secoisolariciresinol, respectively [29, 31]. Sources that are particularly rich in lignan phytochemcials (in order of highest to lowest concentration) are flax, sesame, sunflower and pumpkin seeds. Among all, flax seed is high in lignan content, perhaps the richest source of lignans. However, lignan compounds are also found in many vegetables, fruits and botanical-derived beverages, such as tea and wine.

Tannins

Tannins are phenolic compounds of intermediate to high molecular weight ranging from 500 to $>$ 20,000 Da [7]. The term 'tannin' comes from the capacity of these compounds in transforming animal hides into leather by forming stable tannin-protein complexes with skin collagen [32, 33]. These compounds can form insoluble complexes with carbohydrates and proteins through hydrogen binding of the hydroxyl groups [34]. There exists two main types of tannin viz: hydrolysable tannins and condensed tannins.

Hydrolysable tannins consist of gallic acid polymers and thus forms gallotannins and ellagitannins. Gallotannins are composed of gallic acid units esterified to a central core carbohydrate soy polyol, which is mainly glucose or sorbitol, respectively. Each single gallic acid monomer in gallotannin is called a galloyl unit and is incorporated onto the central core polyol via galloyltransferase [35]. Hydrolysable tannins are easily hydrolysed with both weak aqueous acid and alkali as well as by enzymatic action yielding the central core polyol and the phenolic acid [4, 36].

Condensed tannins (also called proanthocyanadins) are basically high molecular weight flavonoid polymers, in which monomeric unit is a flavanol such as catechin or epicatechin with a flavan-3,4-diol or flavan-4-ol molecule as its precursor [7]. These are typically described by their degree of polymerisation (DP) with DP-1 as monomers and those with DP $=$ 2 to 10 and DP $>$ 10 as oligomers and polymers, respectively [7, 37, 38]. Most of the proanthocyanidins identified occur as oligomers due to the difficulty in analysing highly polymerised complexed molecules [39]. However, proanthocyanidins with an average degree of polymerisation up to 85 in grape skin [40] and 190 in cider apples [41] have been identified.

Polyphenols in Human Health and Diseases

Epidemiological studies have revealed that dietary plant polyphenols exhibit pleiotropic health benefits against development of several chronic diseases which includes cardiovascular diseases (CVDs), cancer, neurodegenerative diseases, ageing, diabetes mellitus and inflammation. Based upon the property of the phenolic groups in polyphenols to accept an electron to form relatively stable phenoxyl radicals and disrupting chain oxidation reactions

in cellular components [42], it is now well established that polyphenol-rich foods and beverages may increase plasma antioxidant capacity. The increased antioxidative capacity of plasma following polyphenol-rich food consumption may be explained either by the presence of reducing polyphenols and their metabolites in plasma, by their effects upon concentrations of other reducing agents (sparing effects of polyphenols on other endogenous antioxidants), or by their effect on the absorption of pro-oxidative food components [43]. Thus, polyphenols may protect cell constituents against oxidative damage and, therefore, limit the risk of various degenerative diseases associated with oxidative stress [44–46]. Further, both antioxidant and prooxidant effects of polyphenols have been elucidated, with contrasting effects on cell physiologic processes. As antioxidants, polyphenols may improve cell survival; as prooxidants, they may induce apoptosis and prevent tumour growth [47]. However, the biological effects of polyphenols may extend well beyond the modulation of oxidative stress.

Polyphenols and Antiplatelet Effects

Cardiovascular disease has a multi-factorial aetiology and it has been recognized for a long time that platelet function is related to the risk of developing atherosclerosis [48]. Activated blood platelets play a central role in this chronic inflammatory condition as they contribute to plaque formation within blood vessels in the early stages of atherogenesis. During this process, platelets become activated upon binding to collagen and von Willebrand factor (vWF) multimers, which are secreted in response to inflammatory stimuli from damaged endothelial cells [49]. Collagen and vWF bind to receptors (glycoprotein VI and integrin $\alpha_2\beta_1$, and the receptor complex glycoprotein Ib/IX/V, respectively) on the platelet surface [50]. The activated platelets then secrete a range of adhesion molecules, such as P-selectin and CD40 ligand, and bind fibrinogen from plasma. Additionally, they synthesize and secrete agonists such as adenosine diphosphate (ADP) and thromboxane A_2, which also induce platelet aggregation and thus amplify and maintain the initial platelet response [50].

Platelet aggregation is a crucial mechanism in the pathogenesis and clinical expression of coronary acute syndrome, and there is extensive evidence that antiplatelet therapy reduces cardiovascular disease risk. Demrow et al., [51] used a coronary artery platelet aggregation model (Folts model) that mimics acute coronary syndromes to demonstrate platelet inhibition following oral administration of red wine to dogs. Similar effects were observed in monkeys as well [52] and these effects have been shown to depend on NO production [53]. Human studies have also demonstrated antiplatelet effects of grape-derived beverages. Freedman et al. [54] demonstrated that grape juice consumption for 14 days decreased platelet aggregation and superoxide production and increased NO production in healthy volunteers. Further, grape juice also inhibited protein kinase C and spared cellular antioxidants. In vitro studies have shown that grape-derived polyphenols inhibit platelet activity and elucidated a number of potential mechanisms. Flavonoids inhibit cyclooxygenase and reduce production of thromboxane A_2. Red wine polyphenols also decrease platelet production of hydrogen peroxide and inhibit activation of phospholipase C and protein kinase C [55].

Polyphenols and their Metabolites Modify Hepatic Cholesterol and Lipoprotein Metabolism: Another Possible Mechanism of Cardioprotection

Studies on animals suggest that polyphenols may reduce cholesterol absorption [56] due to the interaction of these compounds with cholesterol carriers and transporters present across the brush border membrane [57, 58], resulting in less cholesterol being delivered to the liver. Thus, modification of carbohydrate and lipoprotein metabolism could be an additional mechanism by which polyphenols exert its cardioprotective effect. Pal et al. [59] showed that when Caco2 cells were treated with dealcoholized wine, there was a 17 % reduction in apolipoprotein (apo) B48 (primary apolipoprotein responsible for intestinal absorption of dietary fat) production and a 30 % reduction in secretion compared with the control cells, which is attributed to significant decrease in substrate availability. Further, a significant decrease in both free cholesterol (FC) and total cholesterol (TC) concentrations in the dealcoholized red wine-treated cells was observed. The citrus flavonoids, naringenin and hesperitin, were shown to reduce apo B secretion in hepatocytes [60, 61]. This effect was associated with a reduction in cholesteryl ester (CE) mass, a selective decrease in acyl-CoA cholesterol acyltransferase, and microsomal transfer protein (MTP) mRNA abundance accompanied by a decrease in MTP activity. In addition to these findings, naringenin reduced triglyceride secretion into the medium. The mechanism by which polyphenols reduce hepatic apo B production may be through their binding with the plasma membrane transport *p*-glycoprotein, which inhibits cholesterol esterification [62], decreasing the incorporation of cholesteryl ester into nascent VLDL. A lower apo B production rate is strongly correlated with reduced hepatic acyl-CoA cholesterol acyltransferase activity in miniature pigs [63]. Decreases in triglyceride concentrations may also affect overall lipoprotein metabolism. Decreased concentrations of plasma triglyceride can alter the substrate availability in the delipidation cascade, leading to the observed decrease in LDL-cholestrol concentrations as observed in a study reported by [64]. It is evident that grape polyphenols modify

the packaging of VLDL through alteration in hepatic enzyme activity and apo B secretion. These modifications seem to decrease the overall secretion of the VLDL particles and therefore, decrease plasma triglyceride and related apo concentrations. Due to alterations in triglyceride substrate, further modifications in lipoprotein metabolism may occur. It has been reported that lyophilised grape powder decreases plasma triglyceride and subsequently alters the substrate availability in the delipidation cascade, leading to the observed decrease in LDL-cholestrol concentrations [65]. Further, after 4-week treatment period, the lyophilised grape powder treatment induced a significant decrease in cholesteryl ester transfer protein (CETP) activity as well. This decrease in CETP activity may be due in part to the substantial decrease in substrate availability including both plasma triglyceride and LDL-cholestrol. The alteration in TG metabolism may not be the single mechanism driving the hypocholesterolemic effects as evident from reports on dealcoholized red wine. In Hep G-2 cells, dealcoholized red wine was shown to significantly upregulate LDL receptor activity with significantly increased LDL receptor mRNA abundance in a dose-responsive manner. The increase in LDL receptor activity and abundance may be a result of the homeostatic intracellular cholesterol feedback loop.

Thus to summarise, polyphenols and their metabolites were shown to modify hepatic cholesterol and lipoprotein metabolism by decreasing both MTP and acyl-CoA cholesterol acyltransferase activity involved in lipid assembly for VLDL secretion. With the insufficient lipid components, the degradation of apo B-100 is increased. Further, the significant decrease in substrate availability results in a decrease in both VLDL synthesis and secretion. The delipidation cascade also gets altered due to the decrease in VLDL particles in circulation. Alterations to the VLDL particle, including significant decreases in apo E, may induce an increase in LPL activity, and therefore, decrease plasma triglyceride and VLDL concentrations. The VLDL decrease yields a significant decrease in LDL concentrations. Due to the significant alteration in hepatic cholesterol concentrations, the LDL receptor may be upregulated to maintain hepatic cholesterol homeostasis.

Conclusions

The above review of literature in support of polyphenols justifies importance of polyphenols in correlation with their antiplatelet effects as well as modulatory effects on metabolism in circulatory system. It could be infer from above studies that polyphenols are equipped with efficient molecular mechanisms in order to prevent activation of blood platelets that play a central role in this chronic inflammatory condition which leads to plaque formation within blood vessels, so as to prevent cardiac disorders.

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