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Review Article

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Secondary Metabolites of Plants and Their Impact on Health: Case of Polyphenols (A Review)

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Abstract An inverse correlation was noticed between the consumption of plant based food and incidence of cancer and chronic diseases. These virtues are partly attributed to secondary metabolites which are divided into four classes according to their chemical structures. Among them, polyphenols occupy a prominent place. Polyphenols are plant metabolites characterized by the presence of several phenol groups, which derive from L-phenylalanine. They are endowed with multiple biological and pharmacological properties explaining their benefits on human health. Some of them are active due to their antioxidant power; others are involved in the enzymatic detoxification carcinogens in the body. Owing to their diverse biological and pharmacological properties, polyphenols are interesting in cancer prevention and different diseases, including cardiovascular, ophthalmic and inflammatory diseases. Furthermore, phenolic compounds are generally regarded nowadays as desirable components of human food, because of their antioxidant activity. Therefore, they are considered to be of nutraceutical importance.

Keyword: Antioxidants; Polyphenols; cardiovascular; secondary metabolites; nutraceutical importance

Introduction

Polyphenols are the most abundant secondary metabolites in our planet's biosphere. So they are very important compounds. When life emerged out of water onto land, it should adapt to unusual new environmental conditions. This was successfully achieved by the biosynthesis of massive and varied amounts of phenolic compounds acting primarily as efficient UV light screens, thus protecting fragile life against damage from high energy radiation. In the course of evolutionary adaptation phenolic compounds have been selected in particular by sessile plant organisms to take over a further series of important tasks as response to environmental stresses.

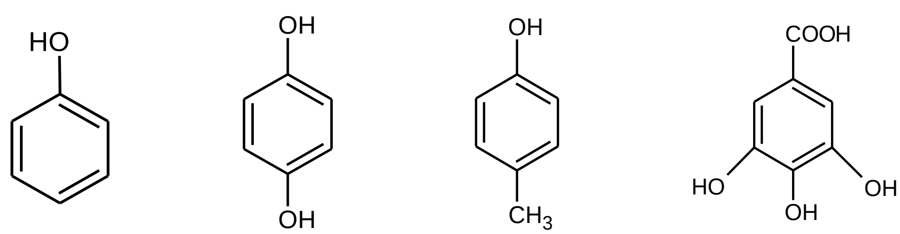
Polyphenols are plant metabolites characterized by the presence of several phenol groups (aromatic rings with hydroxyls), which derive from L-phenylalanine [1,2]. The most important polyphenol classes are phenolic acids, which include polymeric structures, such as hydrolyzable tannins, lignans, stilbenes and flavonoids. Flavonoids include flavonols which as quercetin and kaempferol (the most ubiquitous flavonoids in foods), flavones, isoflavones, flavanones, anthocyanidins (pigments responsible for thecolour of most fruits), flavanols (catechins-monomers and proanthocyanidins-polymers, known as condensed tannins) [3,4]. Some polyphenol hydroxyls are very reactive in a)neutralizing free radicals (-R•) by donating a hydrogen atom (-RH) or an electron (-R•) [5]; b)

chelating metal ions in aqueous solutions[5-7]; c) binding and precipitation of proteins, due to extensively coating of hydrophobic surfaces of peptides and then to cooperative bridge formation [8,9].
Several epidemiological and clinical studies confirm the undeniable role of regular consumption of fruits and vegetables in reducing the risk of cancer and chronic diseases, including cardiovascular disease. These findings seem all the more important that prevention of these diseases has become a strategy extremely interesting. [10]

Definition and classification of polyphenols
The first comprehensive definition of the term “polyphenol”, was proposed by Haslam [11] which attributing it exclusively to water-soluble phenolic compounds having molecular masses of 500 to 3,000–4,000 Da and possessing 12 to 16 phenolic hydroxyl groups and 5 to 7 aromatic rings per 1,000 Da. This original definition of “polyphenols” has broadened considerably over the years to include many much simpler phenolic structures.
They encompass several classes of structurally-diverse entities that are essentially all biosynthesized through either the shikimate/phenylpropanoid or the “polyketide” acetate/malonate secondary metabolic pathways [12], or both. All plant phenolic compounds arise from a common intermediate, phenylalanine, or a close precursor, shikimic acid. Polyphenols may be classified into different groups as a function of the number of phenol rings that they contain and on the basis of structural elements that bind these rings to one another. According to some authors, the main classes include simple phenols, phenolic acids, flavonoids, stilbenes and lignans [13]. But for a detailed classification we can divide polyphenols into two major families: the non-flavonoids (simple phenols, phenolic acids, stilbenes and lignans) and flavonoids (flavones, flavonols, isoflavones, flavanes, flavanones, chalcones, flavonols, anthocyanidins and tannins).

- **Simple phenols**

Very rare in nature, simple phenols are derived six carbonbenzene ring onto which are grafted one or more hydroxyl groups. We distinguish in this group hydroquinol, cresol and shikimic acid.



Phénol Hydroquinol p-crésol Acide shikimique

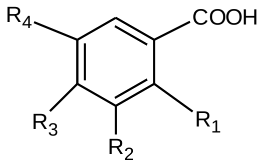
Figure 1: Structure of simple phenols

- **Phenolic Acids**

Phenolic acids are found abundantly in foods and divided into two classes: derivatives of benzoic acid and derivatives of cinnamic acid. The hydroxybenzoic acid content of edible plants is generally low. The hydroxycinnamic acids, commonly called phenylpropanoids, are more common than hydroxybenzoic acids. Some members of this huge class of natural products, usually bearing two mono-trihydroxyphenyl units, can serve as precursors to oligo- and polymeric phenolic systems. The general phenylpropanoid metabolism furnishes a series of hydroxycinnamic acids differing from one another by the number of hydroxy and methoxy groups on their phenyl units (*i.e.*, *p*-coumaric, caffeic, ferulic and sinapic acids). These monophenolic carboxylic acids are often found esterified to polyols. Through hydration, esterification, and phenolic oxidative coupling reactions, caffeic acid also gives rise to oligomeric structures.

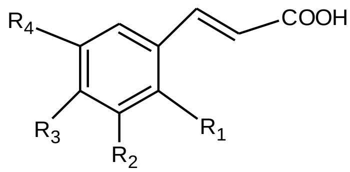
- **hydroxybenzoic acid**

$R_1 = R_2 = R_3 = R_4 = H$ benzoic acid



$R_1 = R_2 = R_4 = H, R_3 = OH$	p-hydroxybenzoic acid
$R_1 = R_4 = H, R_2 = R_3 = OH$	Protocatechuic acid
$R_1 = R_4 = H, R_2 = OCH_3, R_3 = OH$	Vanillic acid
$R_1 = H, R_2 = R_3 = R_4 = OH$	Gallic acid
$R_1 = H, R_2 = R_4 = OCH_3, R_3 = OH$	Syringic acid
$R_1 = OH, R_2 = R_3 = R_4 = H$	Salicylic acid
$R_1 = R_4 = OH, R_2 = R_3 = H$	Gentisic acid

- **hydroxycinnamic acid (phenylpropanoids)**

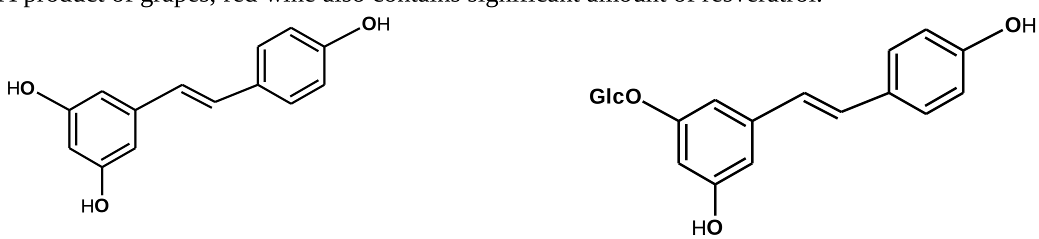


$R_1 = R_2 = R_3 = R_4 = H$	cinnamic acid (non-phenolic)
$R_1 = OH, R_2 = R_3 = R_4 = H$	O-coumaricacid
$R_1 = R_4 = H, R_2 = R_3 = OH$	caffeic acid
$R_1 = R_4 = H, R_2 = OCH_3, R_3 = OH$	Ferulic acid
$R_1 = R_2 = R_4 = H, R_3 = OH$	O-coumaric acid
$R_1 = H, R_2 = R_4 = OCH_3, R_3 = OH$	sinapic acid

Figure 2: Structure of the main phenolic acids

- **Stilbenes**

Stilbenes contain two phenyl moieties connected by a two-carbon methylene bridge. Occurrence of stilbenes in the human diet is quite low. Most stilbenes in plants act as antifungal phytoalexins, compounds that are synthesized only in response to infection or injury. The most famous example of this class is the phytoalexin trans-resveratrol (3,5,4'-trihydroxy-trans-stilbene), which has been the center of much scientific attention and media exposure following its biological evaluation as a cancer chemopreventive [14-16]. It was largely reported in grapes and sorghum grains [17,18]. A product of grapes, red wine also contains significant amount of resveratrol.



Trans-resveratrol Trans-piceid

Figure 3: Main stilbenes found in plants

- **Lignans**

Lignans are diphenolic compounds that contain a 2,3-dibenzylbutane structure that is formed by the dimerization of two cinnamic acid residues. Several lignans, such as secoisolariciresinol, are considered to be phytoestrogens. The richest dietary source is linseed, which contains secoisolariciresinol (up to 3.7 g/kg dry weight) and low quantities of matairesinol [19].

- **Flavonoids**

Flavonoids comprise the most studied group of polyphenols. This group has a common basic structure consisting of two aromatic rings bound together by three carbon atoms that form an oxygenated heterocycle (Figure 4). More than 4,000 varieties of flavonoids have been identified, many of which are responsible for the attractive colours of the flowers, fruits and leaves [20]. Based on variations in the type of heterocycle involved, flavonoids may be divided into several subclasses: flavonols, flavones, flavanones, isoflavones, chalcones, flavanols, anthocyanins isoflavones and tannins. The individual differences within each group arise from the variation in number and arrangement of the hydroxyl groups and their extent of alkylation and/or glycosylation [13]. The C_{15} hydrocarbon skeleton (sequence C_6-C_3-C_6) of flavonoids is the basis of many thousands of molecules which are grouped into different classes based on their degree of oxidation.

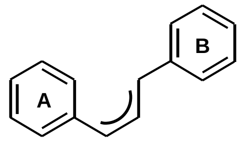


Figure 4: Hydrocarbon skeleton of flavonoids

This can provide a skeleton with 3 cycles (Table 1) which is the basis of polyphenolic structures of biological and technological importance as anthocyanins (red pigments whose color depends on the pH of the medium), flavones and flavan that lead to the formation of condensed tannins. It is the central structure of the heterocycle which allows bundling of flavonoids on the basis of their color. Anthocyanidins, usually red, are characterized by the introduction of the central heterocycle enabling the protonation of the oxygen in an acid medium, giving the optimal staining of flavylium cation. Flavones have a partial unsaturation of cycle C and flavanols a saturation of cycle C. These polyphenols give a yellow coloration.

The heterocyclic six-membered C-ring is sometimes replaced by a five-membered ring (e.g., aurones) or the acyclic form and gives a colorless schalcone structure. Flavonoids occur widely as glycosylated monomers or as flavan-3-ol oligomers (proanthocyanidins = condensed tannins).

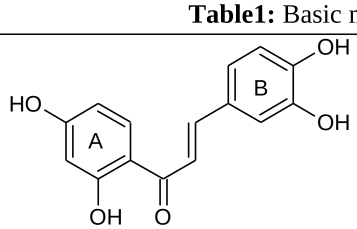
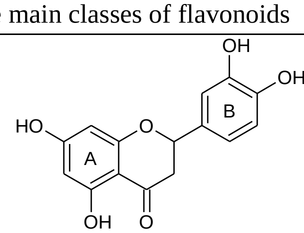
In flavonols the carbon C_3 of the heterocycle is always glycosylated. Frequently, the position 7 of the A ring is also glycosylated but never the position 5. The type of sugar attached to this structure at one or more positions can be a monosaccharide (often glucose), a diholoside (galactose, arabinose, rhamnose...associated with glucose) or acylations sugar-organic acids (caffeic, coumaric acid, malic) more or less complex. These acylations increase greatly the stability of polyphenol but modify its physicochemical properties (color). Flavonols which have more hydroxyls groups at position 6 or 8 color some flowers in yellow [21,22].

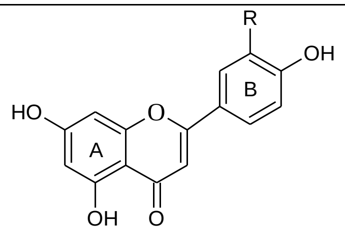
Flavanones do not contain OH groups in position 3, and are rather similar structures with the flavonols. In this category, we can arrange the flavonoids responsible for the bitter taste of some grapefruit, lemons, orange: naringin (naringénol related to glucose and rhamnose), hesperidin, Butine, fustin [23].

Flavones are distinguished by the number and position of hydroxyl, methoxyl and other piggyback on rings A and B (Table 1). Ring A is generally substituted by hydroxyl groups at positions 5 and 7 and more rarely by methoxyl groups. Ring B is often substituted with one, two or three hydroxyl groups or methoxyl.

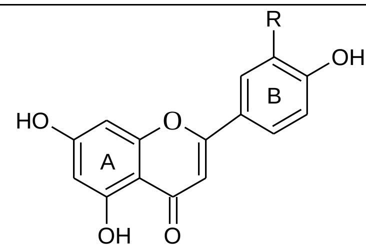
Anthocyanins are natural phenolic molecules from the secondary metabolism of plants with a common structureanthocyanidinC_6-C_3-C_6 (Table1). Their properties vary according tothe nature of the oxygenated heterocycle central. The basic structure of anthocyanins is the flavyliumcation (red chromophore), or phenyl-2-benzopyrylium. This cation is an oxonium ion which is characterized by a red color in an acid medium (pH <3) with a maximum absorption around 520 nm. The very high reactivity of flavyliumnucleus with nucleophiles is a factor of the relative instability of anthocyanidins and explains their rarity in plant tissues as anthocyanidins. They are generally found in the form of glycosides, and this is known as anthocyanins [24-26]. Glycosylations encountered in anthocyanins give them their solubility and stability. In total, eighteen anthocyanidins are currently known, and the six most widespread in the plant kingdom are Cyanidin, pelargonidin, Delphinidin, Peonidin, malvidin and Petunidin [27]. Many studies have contributed to distinguish two major different groups of anthocyanins which differ depending on the nature of the substituent in position 3: 3-oxyanthocyanins and 3-deoxyanthocyanins. The 3-deoxyanthocyanins very rare in plant kingdom are far more stable than their homolog hydroxylated in position 3, which makes them potential food coloring compounds [28].

Table1: Basic molecular skeleton and the main classes of flavonoids

 Chalcones: buteine	 Flavanones: naringenin (R=H); eriodyctiol (R=OH)

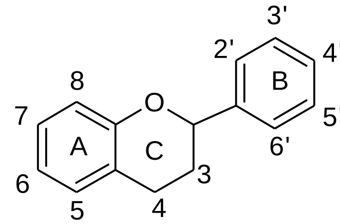


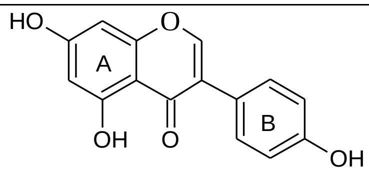
Flavonols: Kaempferol (R=H)
quercetin (R=OH)



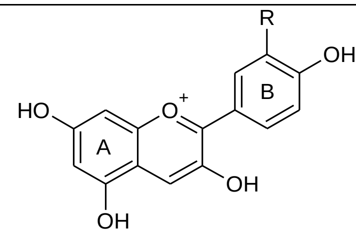
Flavones: apigenidin (R=H)
Luteolin (R=OH)

Basic molecular skeleton of flavonoids with the conventional numbering

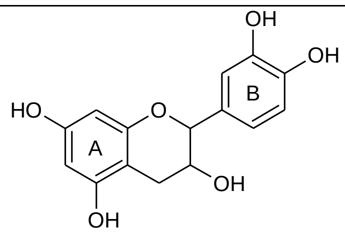




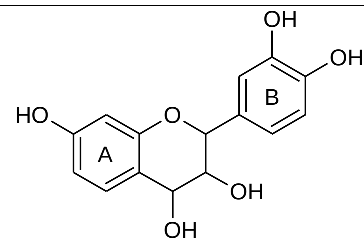
Isoflavones: genistein



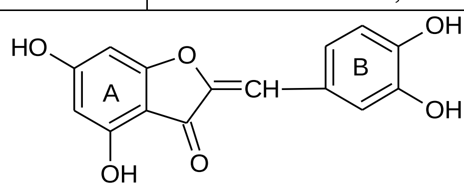
Anthocyanidins: pelargonidin (R=H)
Cyanidin (R=OH)



Flavan-3-ols: catechuin, épichatechuin



Flavan-3,5-diols: leucorobinetinidine



Aurones: aureusidine

Biological and pharmacological properties of polyphenols

The biological activity of plant extracts is mainly due to their content of secondary metabolites [29]. Behalerao and kelkar were reported that a majority of the ascribed biological effects of *Cassia fistula* extracts have been attributed to their secondary metabolite composition [30]. Pepsi *et al*. showed that the medicinal properties of some aquatic plants were linked to their polyphenol content [31]. Similarly, Alitonou et *al*., Aweng et *al*. and Agbangan et *al*. showed respectively that the biological activities of essential oils of *Eucalyptus Torelliana,* and *Vitex Trifolia* and ethanol extract of *Sorghum caudatum* were mainly due to their polyphenol content [32-34]. Several studies have shown that biological properties of polyphenols include antioxidant [35], anticancer [36], and anti-inflammatory [37] effects. Otherwise, chlorogenic acids (CGAs), one of the most important class of dietary polyphenols, have a wide range of fascinating biological activities including anti-HIV, anti-viral, anti-plasmodic, inhibit glucose transporters or show opioid receptor activity. The studies carried out in recent decades have confirmed the antibacterial and anti-Cariogenic action of polyphenols [38-46]: they may reduce bacterial growth rate and adherence to tooth surface, and also can perform inhibitory effects on the enzymatic activity of glucosyltransferase and amylase [47-53]. But most of these activities are related to the chemical structure of the compounds [54] and therefore to their membership family. Thus, numerous studies have established relationships between the chemical structures of flavonoids and their scavenger ability of free radicals [55, 56, 57-61].

Flavonoids

The main property initially recognized to flavonoids is being "veno-active." They decrease the permeability of blood capillaries and strengthen their resistance. This property has earned them, also known as "vitamin P". These phenolic compounds are also antioxidants that can scavenge free radicals (FR). These appear in several situations such as oxidative metabolism of oxygen, anoxia, inflammation and auto-oxidation of lipids [6, 8]. Indeed, during oxidative stress, free radical species of control will attack targets such as bioactive proteins (thereby altering cell receptors and enzymes), and nucleic acids. These alterations favor the occurrence of deleterious mutations causing various cancers. The action of free radicals in lipids, including LDL particles in the vascular intima, is the premium mavens in the cascade atherogenic [31].

Anthocyanins

The antioxidant effect of anthocyaninsis partly explained by the free radical scavenging and metal chelation. In addition, the cyanidol forms a pigmentation complex with DNA, thus protecting this molecule critical oxidative damage [20]. Anthocyanins inhibit proteolytic enzymes of collagen degradation (elastase, collagenase), which explains their vasoprotective and anti-edematous properties. It is, moreover, veno-active compounds endowed with a Vitamin "P" property [6]. Anthocyanins blocknitric oxide (NO) production from neutrophils during the early phase of inflammation and are considered as anti-inflammatory molecules [20]. Anthocyanins have therapeutic properties, especially in ophthalmology in relation to their property to improve acuityvisuelle [62]. In fact, anthocyanins are mainly used in progressive myopiain retinopathy and improve night vision. The action on the progressive myopia is particularly marked in young subjects. In most cases, along-term treatment can stabilize the myopia, and of tendecrease. As forretinopathy, actions are sharper observed in hypertensive retinopathy and diabetic origin. The best results are obtained in cases of conjunctival haemorrhage and retinal which are quickly absorbed. It seems that the effect of anthocyanins on the vascular wall partly explains this action. The action of anthocyanins on night vision is now well known, it is due to the increase in the rate of regeneration of retinal purple or érythropsine. More recent studies focus on the antioxidant power of anthocyanes [63] and in particular the role played by these phenolic compounds as therapeutic agents in the treatment of tumors [64] such as human melanoma [65] or colon cancers [66].

Tannins

The tannins in turn, are endowed with antioxidant power. Thus hydrolysable tannins inhibit lipid peroxidation and condensed tannins inhibit the formation of superoxide [6]. Catechols, identified in tea and red sorghum, scavenge free radicals, chelate metal ions and preserve other antioxidants such as vitamin E [1]. These polyphenolic compounds inhibit the enzyme activity of the protein kinase C, the 5-lipoxygenase enzyme and angiotensin converting [6] and are active on thermogenesis. Epicatechin gallate, abundant in green tea, stimulates thermogenesis and promotes oxidation of dietary fat [9]. Some tannin also has vitamin "P" properties [6].

Stilbenes

As constituents of small fruits such as grapes, berries and their products, stilbenes are under intense investigation as cancer chemopreventive agents. One of the best-characterized stilbenes, resveratrol, has been known as an antioxidant and an anti-aging compound as well as an anti-inflammatory agent. Stilbenes have diverse pharmacological activities, which include cancer prevention, a cholesterol-lowering effect, enhanced insulin sensitivity, and increased lifespan [67]. The anticancer properties of resveratrol derived not only from its antioxidant [6,15], but also from its pro-apoptotic and antiproliferative properties[15]. Its vasodilatory effects [26], antiplatelet [6] and its ability to prevent lipid peroxidation [26] confer to this family of molecules its cardioprotective properties. It is, moreover, an anti-inflammatory molecule that inhibits cyclooxygenase in its both forms (Cox 1 and Cox 2) [22].

Beneficial effects of polyphenols on health

Associations between polyphenol intake or the consumption of polyphenol-rich foods and protection against degenerative diseases have been examined in several epidemiological studies.

Polyphenols are secondary metabolites of plants and are generally involved in defense against ultraviolet radiation or aggression by pathogens. In the last decade, there has been much interest in the potential health benefits of dietary plant polyphenols as antioxidant. Epidemiological studies and associated meta-analyses strongly suggest that long term consumption of diets rich in plant polyphenols offer protection against development of cancers, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases.

With phenolic compounds it is interesting to note that humans are likely to have lost the ability to synthesize vitamins, which include several terpenoids and methylated phenols, because the ubiquity of these micronutrients in our diet made it more advantageous in evolutionary terms to sequester them from food rather than synthesize them [68]. The same argument has been made for all dietary antioxidants, including many nonvitamin phytochemicals [69], and this proposition could be extended to include the nonantioxidant properties of groups of phytochemicals that occurred as part of our natural ancestral diet. This would largely accommodate the phenolic compounds, and flavonoids in particular, that are ubiquitous in plant foods. It may be relevant that most phenolic compounds have low parent-molecule bioavailability but still exhibit in vivo bioactive effects [70,71].

Polyphenols are the most abundant antioxidants in our diet and are widespread constituents of fruits, vegetables, cereals, dry legumes, chocolate, and beverages, such as tea, coffee or wine. Experimental studies on animals or cultured human cell lines support a role of polyphenols in the prevention of cardiovascular diseases, cancers, neurodegenerative diseases, diabetes or osteoporosis. Clinical studies on biomarkers of oxidative stress, cardiovascular disease risk factors, and tumor or bone resorption biomarkers have often led to satisfactory results. Epidemiological studies have repeatedly shown an inverse association between the risk of myocardial infarction and the consumption of tea and wine or the intake level of some food particular rich in flavonoids. The consumption of tea and a moderate consumption of wine have been regularly associated to a lower risk of myocardial infarction. Cconsumption of foods rich in polyphenols reduces the development of many pathologies, such as cancer, cardiac ischemia, atherosclerosis and hypertention [72-83]. Polyphenols also have anti-diabetic properties [83]. They have also been described as antiplatelet agents, antiallergens and anti-tumors [72]. Polyphenols are indeed capable of preventing the oxidation of LDL (low density lipoproteins) [84], of inhibiting the proliferation of vascular smooth muscle cells [85] to prevent platelet aggregation [86] and to promote the release of vascular smooth muscle cells [87,88]. Numerous laboratory studies have investigated the direct effects of red wine polyphenols on vessels and vascular cells [80] and their *in vivo* effects on the prevention of hypertensive development in rats [89]. As antioxidants, polyphenols may protect cell constituents against oxidative damage and, therefore, limit the risk of various degenerative diseases associated to oxidative stress. Numerous studies on animal models have shown that, when added to the diet, they limit the development of cancers, cardiovascular diseases, neurodegenerative diseases, diabetes and osteoporosis.

Several studies have focused on the impact of consumption of flavonoid-rich beverages and especially quercetin (10-25 mg / L) [90]. The latter has antioxidant, anti-aggregating and vasodilating effects that may explain its cardioprotective effects [91, 92]. Similarly, the ingestion of flavonoids, mainly in tea, onions and apples, has been associated with a considerable reduction in mortality from cardiovascular diseases [92]. The consumption of quercetin in onions (0.3 mg / g fresh mass) and apples (1 mg / g fresh skin mass) has been shown to be inversely correlated with the risk of lung cancer [93, 90].

Tannins are polyphenols that occur widespread in plant-based food. They are considered to be part of the plant defense system against environmental stressors. Tannins have a number of effects on animals and humans. Catechols, the basic structural units of tea catechic tannins, exert a cardioprotective activity, thanks to their antioxidant, anti-inflammatory and anti-thrombotic properties [9, 94]. They are also effective in the prophylaxis of certain cancers such as skin and lung cancer [95]. Green tea consumed at a rate of 2 to 4 cups per day (one cup provides 300 to 400 mg of polyphenols) can replicate the effects of epicatechol gallate on thermogenesis, thus contributing to a lower incidence of obesity [96].

In an overview presented by Hertog and Hollman the potential health effects of quercetin and other flavonols and flavones were summarized Experimental studies in animals suggest that dietary quercetin, at relatively high doses, could inhibit the initiation and development of tumors in humans. These results are supported by *in vitro* studies showing that quercetin inhibited the growth of isolated human tumour cell lines. In fate, atherosclerosis is a condition that results from the gradual build-up of fatty substances, including cholesterol, on the walls of the arteries. This build-up, called plaque, reduces the blood flow to the heart, brain and other tissues and can progress to cause a heart attack or stroke. This process is commonly referred to as hardening of the arteries. An elevated plasma low density lipoprotein (LDL) concentration is a primary risk factor for the development of atherosclerosis and coronary artery diseases. Reactive oxygen species generated through lipid peroxidation can oxidatively modify i.e. oxidize the amino acid residues of LDL and this can initiate the atherosclerotic process. Flavonoids seem to suppress LDL oxidation and inflammatory progression in the artery wall. A Japanese study reported an inverse correlation between flavonoid intake and total plasma cholesterol concentrations, other clinical studies, as mentioned earlier, stated that flavonoid intakes protect against coronary heart disease.

Conclusion

As a result of this bibliographic work we can now define precisely the polyphenol theme. Indeed, the meaning of the chemical term “phenol” includes both the arene ring and its hydroxyl substituent(s), and the term “polyphenol” should be confined, in a strict chemical sense, to structures bearing at least two phenolic moieties, independently of the number of hydroxyl groups that they each bear. Moreover, many natural products of various biosynthetic origins do not contain more than one phenolic unit. It is, for example, the case for many alkaloids derived from the amino acids phenylalanine and tyrosine. The term “polyphenol” should be used to define compounds exclusively derived from the shikimate/phenylpropanoid and/or the polyketide pathways, featuring more than one phenolic unit and deprived of nitrogen-based functions. Nowadays, these compounds play an inescapable role in the life of man. The studies carried out in recent decades have confirmed several roles of polyphenols: they may reduce bacterial growth rate and adherence to tooth surface, and also can perform inhibitory effects on the enzymatic activity of glucosyltransferase and amylase. Moreover, polyphenols largely occur in flowering plants and could be used at a reasonable cost in the preparation of specific remedies. Flavonoids seem to be particularly promising anticariogenic molecules. The knowledge of polyphenols as bioactive secondary metabolites is now well acquired and is the origin of our increased interest in recent years in these compounds in the field of nutrition and pharmacology. Remarkable results have already been obtained for some compounds but much work remains to be done in this area because the approaches often remain comprehensive and take into account only the set of compounds present in an extract or food from the plant world. It will be essential in the future to clarify the qualitative and quantitative composition of each phenolic compound to test them individually. This should help to understand the mode of action of each and evaluate their eventual synergy or antagonism effects. Research work on the relationships between chemical structure and biological activity of these compounds are also required.

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