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REVIEW ARTICLE

Phenolic compounds and their health benefits: A review

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Abstract

Phenolic compounds, ubiquitous in plants, are essential part of human diet. Major polyphenolic compounds found in plants are flavonoids, catechins, epigallocatechin-3-gallate (EGCG), flavonones, iso-flavones, flavanols, anthocyanins, phenolic acids, stilbenes, flavonoids, chalcones, lignans etc. These compounds are secondary plant metabolites and possess antimicrobial, antiviral and anti-inflammatory properties along with high antioxidative activity. These properties make polyphenols interesting for the treatment of various diseases like inflammation, cancer and also used for anti-ageing purposes in cosmetic formulations as well as have nutraceutical applications. The antioxidative activity of phenolic compounds depends on their structure, in particular the number and position of the hydroxyl groups and the nature of substitutions on the aromatic rings. Fruits, vegetables and beverages are the chief sources of phenolic compounds in the human diet. This review focused on plant polyphenols, taking into consideration aspects relative to their structure, botanical sources, action, bio-availability as well as their potential health benefits.

Keywords: Polyphenols, antioxidant, free radical scavenger, health benefits.

Abbreviation: EGCG -Epigallocatechin-3-gallate, PIN- Prostate intraepithelial neoplasia, IGF-1-Insulin like growth factor-1, COX- Cyclo-oxygenase, BBB-Blood-brain barrier.

1. Introduction

Phenolic compounds are secondary metabolites that are derivatives of the pentose phosphate, shikimate and phenylpropanoid pathways in plants. They are essential to the physiology of plants, because of their involvement in various important functions (growth, structure, defense, pigmentation, lignifications etc.). The majority of polyphenols are synthesized by the highly branched phenyl propanoid pathway, which is responsible for the biosynthesis of a large number of chemical compounds with considerable structural diversity. They are largely found in fruits, vegetables, cereals and beverages (Huang *et al.,* 2005). Chemically, polyphenols have a common structure of flavone. Polyphenols may be derivatives such as flavonoids, catechins, epigallocatechin-3-gallate (EGCG), flavonones, isoflavones, flavanols, dalbergin, anthocyanins, proanthocyanidins, anthocyanidins, phenolic acids, phenolic alcohols, polyphenolic amides (avenanthramide, capsaicinoid), stilbenes, flavonoids, chalcones, lignans and other non-flavonoids such as resveratrol, rosemaric acid, gingerol, ellagic acid, secoisolariciresinol, metaresinol, valoneic acid dilactone, lignans, curcumin, and hydrolyzable tannins (gallic acid, ellagic acid, rosmarinic acid). Inside each of these classes, the variations around the basic chemical skeleton essentially concern the degree of oxidation, hydroxylation, methylation, glycosylation and the possible connections to other molecules (Munin and Levy, 2010). They are a diverse group of chemicals having one feature in common that is the presence of at least one aryl ring to which a minimum one hydroxyl group is attached. Fontana *et al.* (2002) reported that plant phenolics and terpenoids are being widely used because of their strong antimicrobial property against food borne pathogens and therefore, could be applied as novel preservatives in the food industry. In food, polyphenols may contribute to the bitterness, astringency, color, flavor, odor and oxidative stability. Phenolic compounds exhibit a wide range of physiological properties, such as anti-allergenic, anti-artherogenic, anti-inflammatory, anti-microbial, antioxidant, anti-thrombotic, cardio-protective and vasodilatory effects (Arts *et al.*, 2005; Graf *et al.*, 2005). Polyphenols can act as metal chelators which adds to the antioxidant effects of these compounds through inhibition of transition metal-catalyzed free radical formation (Jomova *et al.,* 2010). They also act as inhibitor of pre-harvest seed germination (Bravo 1998; Haslam, 1998). Polyphenols and other food phenolics are the subject of increasing scientific interest because of their possible beneficial effects on human health. These compounds are present in all plant foods but their type and levels vary enormously depending on the plant, genetic factors and environmental conditions (Etherton *et al.,* 2002).

2. Structure and Classification of Polyphenols

More than 8,000 polyphenolic compounds are identified in various plant species. Structurally, phenolic compounds comprise an aromatic ring, bearing one or more hydroxyl substituent and ranged from simple phenolic molecules to highly polymerized compounds (Bravo, 1998). Plant phenolic compounds have common intermediate (i.e. phenylalanine, or a close precursor, shikimic acid). Primarily they occur in conjugated forms with one or more sugar residues linked to hydroxyl groups, although direct linkages of the sugar (polysaccharide or monosaccharide) to an aromatic carbon also exist. Association with other compounds like carboxylic and organic acids, amines, lipids and linkage with other phenol is also common (Kondratyuk *et al.,* 2004). Polyphenols are classified on the basis of the number of phenol rings that they contain the structural elements that bind these rings to one another (Fig 1). They are broadly divided in four classes: phenolic acids, flavonoids, stilbenes and lignans. Phenolic acids are further divided into hydroxycinnamic acid (HCA) and hydroxybenzoic acid (HBA). Phenolic acids account for about a third of the polyphenolic compounds in our diet and are found in all plant materials, but are particularly abundant in acidic fruits. Caffeic acid, gallic acid, ferulic acid are some common phenolic acids. Flavonoids are most abundant polyphenols in human diet and share a common basic structure consisting of two aromatic rings, which are bound together by three carbon atoms that form an oxygenated heterocycle. Bio-genetically, one ring usually arises from a molecule of resorcinol and other ring from the shikimate pathway. Stilbenes contain two phenyl moieties connected by a two carbon methylene bridge and the most extensively studied stilbene is resveratrol. Mostly, stilbenes in plants act as anti-fungal phytoalexins, compounds that are synthesized only in response to infection or injury. Lignans are diphenolic compounds which contain a 2, 3-dibenzylbutane structure that is formed by the dimerization of two cinnamic acid residues (Spencer *et al.,* 2008). Chemical structure of the most common polyphenols and their botanical sources are summarized in Table 1.

2.1. Phenolic Acids

Phenolic acids are widely dispersed in plant kingdom. They contain two distinguishing constitutive carbon frameworks, hxydroxycinnamic (C_6C_3) and hydroxybenzoic (C_6C_1) structure. The hydroxybenzoic acid content of edible plants is generally low, with the exception of certain red fruits, black radish and onions which have high concentration (Shahidi *et al.,* 1995). The hydroxycinnamic acids are more common than hydroxybenzoic acids and consist chiefly of p-coumaric, caffeic, ferulic and sinapic acids (Han *et al.,* 2007). Phenolic acids have antioxidant properties due to their high redox potential, which allows them to act as reducing agents and singlet oxygen quencher (Ignat, 2011).

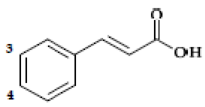
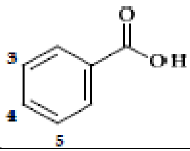
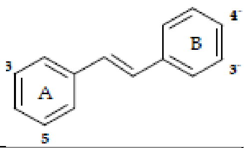
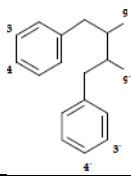
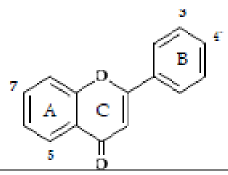
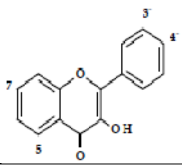
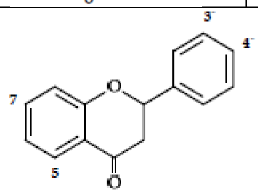
2.2. Flavonoids

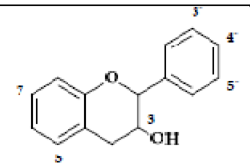
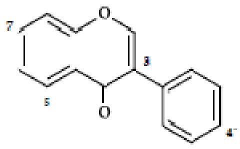
Flavonoids constitute the largest class of phenolic compounds with more than 3,000 structures. These consist of two aromatic rings bound together by three carbon atoms that form an oxygenated heterocycle (Tsao, 2010**).** Due to the hydroxylation pattern and variations in the chromane ring (Ring C), flavonoids can be further divided into different sub-groups such as anthocyanins, flavan-3-ols, flavones, flavanones and flavonols (Merken and Beecher, 2000) of which flavones and flavonols are most widely occurring. 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 (Spencer *et al.,* 2008). More than 4,000 varieties of flavonoids have been identified which are responsible for the attractive colours of the flowers, fruits and leaves (Groot and Rauen, 1998). Quercetin, epicatechin, myricetin, catechins etc. are some of the common flavonoids.

2.2.1 Flavonols

Flavonoids are the largest class of polyphenols. Chemically, they may be defined as a group of polyphenolic compounds consisting of substances that have two substituted benzene rings connected by the chain of three carbon atoms and an oxygen bridge. Quercetin and kaempferol are the ubiquitous flavonoids in foods. Flavonols accumulate in the outer and aerial tissues (skin and leaves) in fruits because their bio-synthesis is stimulated by light. In leafy vegetables such as lettuce and cabbage, the glycoside concentration is $\geq$10 times as high in the green outer leaves as in the inner light-colored leaves (Herrmann, 1999).

Table 1: Chemical structure of the most common polyphenols and their botanical sources

Class	Main structure	Compound	Plant source	Reference
Phenolic acid	Hydroxycinnamic acid (HCA) 	ferulic acid 4–OH; 3–OCH3 caffeic acid 3,4–OH chlorogenic acid (5-O-caffeoylquinic acid) rosmarinic acid (α-O-caffeoyl-3,4 dihydroxyphenyll acid)	*Citrus sinensis* *Pinus maritima* *Ocimum basilicum* *Helianthus annuus* *Coffea arabica* *Ilex paraguariensis* *Rosmarinus officinalis* *Melissa officinalis*	(Swatsitang *et al.*, 2000;Virgili *et* 2000) (Kwee and Niemeyer, 2011; Weis *al.*, 2009) (Marques and Farah, 2009) (Petersen and Simmonds, 20 Weitzel and Petersen, 2011)
	Hydroxybenzoic acid (HBA) 	p-HBA 4–OH gallic acid 3, 4, 5–OH	*Daucus carota* *Vitex negundo* *Quercus robur* *Hamamelis virginiana*	(Sircar&Mitra, 2009; Guha *et* 2010) (Mämmelä *et al.*, 2000; Wang *et al.*, 2003)
Stilbene		resveratrol 3,5,4'-OH piceatannol 3,5,3',4'-OH	*Vitis vinifera* *Polygonum cuspidatum* *Vitis vinifera* *Euphorbia lagascae*	(Pascual-Martí *et al.*, 2001; Chen *al.*, 2001) (Kim *et al.*, 2009; Duarte *et* 2008)
Lignan		secoisolariciresinol 4,9,4',9'-OH 3,3'–OCH3 isotaxiresinol 4,3',4'–OH 3–OCH3	*Linumu sitatissimum* *Secale cereale* *Taxusy unnanensis* *Taxus wallichiana*	(Li *et al.*, 2008; Smeds *et al.*, 2009) (Banskota *et al.*, 20 Chattopadhyay *et al.*, 2003)
Flavone		Apigenin 4',5,7-OH luteolin 3',4',5,7-OH	*Matricariare cutita* *Achillea millefolium* *Cynara scolymus* *Thymus vulgari*	(Švehlíková and Repčák, 2006; Trumbeckaite *et al.*, 2011) (Mulinacci *et al.*, 2004; Bazylko Strzelecka, 2007)
Flavonol		Quercetin 3',4',3,5,7-OH kaempferol 4',3,5,7-OH	*Sambucus nigra* *Betula pendula* *Ginkgo biloba* *Moringa oleifera*	(Keinänen and Julkunen-Tiitto, 1998; Verberic *et al.*, 2009) (Beek and Montoro, 2009;Verma *al.*, 2009)
Flavonone		Naringenin 4',5,7-OH hesperetin 3',5,7-OH 4'-OCH3	*Citrus paradisi* *Humulus lupulus* *Citrus limon* *Citrus sinensis*	(Kanaze *et al.*, 2003; Helmja *et* 2007) (González-Molina *et al.*, 2010; Kl *et al.*, 2010)

Flavanol		Catechin 4',5',3,5,7-OH gallocatechin 3',4',5',3,5,7-OH	*Quercus petraea* *Potentilla erecta* *Hamamelis virginiana* *Camellia sinensis*	(Vivas *et al.,* 2006; Tomczyk Latté, 2009) (Dauer *et al.,* 2003; Ashihara *et* 2010)
Isoflavonoid		Daidzein 4',7-OH genistein 4',5,7-OH	*Glycine max* *Trifolium pratense* *Glycine max* *Genista tinctoria*	(Peng *et al.,* 2004; Beck *et al.,* 200 (Rimbach *et al.,* 2008; Rigano *et* 2009)

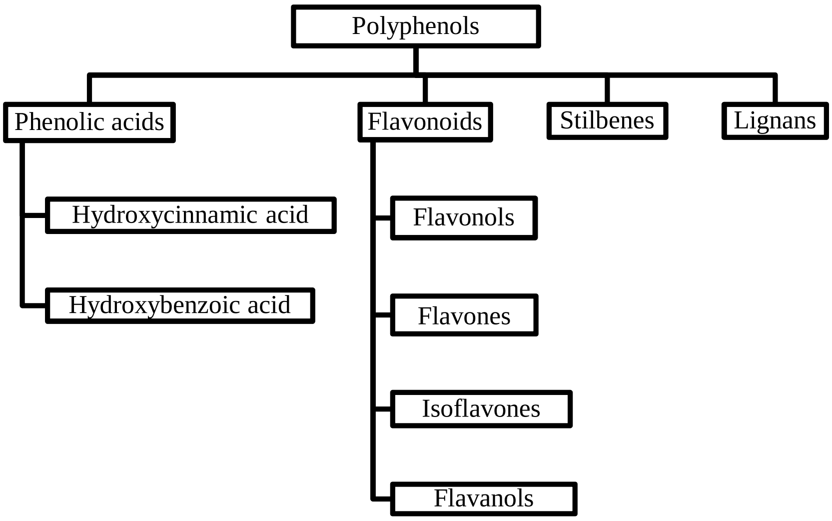


Fig 1: Classification of major plant polyphenols

2.2.2 Flavones

Flavones are much less common than flavonols in fruits and vegetables. Flavones consist chiefly of glycosides of luteolin and apigenin. The only important edible sources of flavones identified to date are parsley and celery. Cereals such as millet and wheat contain C-glycosides of flavones (King, 1962; Sartelet *et al.,* 1996). The skin of citrus fruits contains large quantities of polymethoxylated flavones like tangeretin, nobiletin, and sinensetin (up to 6.5 g/L of essential oil of mandarin (Parvathy *et al.,* 2009). These polymethoxylated flavones are the most hydrophobic flavonoids (Tsao *et al.,* 2003). The main aglycones are naringenin in grape fruit, hesperidins in oranges and eriodictyol in lemons. In human foods, flavnones are found in tomatoes and certain aromatic plants such as mint, but they are present in high concentrations only in citrus fruits. Flavanones are generally glycosylated by a disaccharide at position 7, either a neohesperidose, which imparts a bitter taste (such as to naringin in grape fruit) or a rutinose, which is flavorless. Orange juice contains between 200 and 600 mg hesperidin/L and 15–85 mg narirutin/L and a single glass of orange juice may contains between 40 and 140 mg flavanone glycosides (Tomas-Barberan *et al.,* 2000).

2.2.3. Isoflavones

Isoflavones have structural similarities to estrogens i.e. hydroxyl groups in the C7 and C4 positions like estradiol molecule. Genistein and daidzein are the two main isoflavones found in soya along with glycetein, biochanin A and formononetin. They have pseudo-hormonal properties because of the ability to bind to estrogen receptors and so that they consequently classified as phytoestrogens. These isoflavones are found in 4 forms: aglycone, 7-O-glucoside, 6-O-acetyl-7-O-glucoside and 6-O-malonyl-7-O-glucoside (Coward *et al.,* 1998). The 6-O-malonyl-glucoside derivatives have an unpleasant, bitter and astringent taste. They are sensitive to heat and are often hydrolyzed to glycosides during the course of industrial processing, as in the production of soya milk (Kudou *et al.,* 1991).

2.2.4 Flavanols

Flavanols exist in monomer (catechins) as well as polymer form (proanthocyanidins). Catechins are found in many types of fruits (apricots, which contain 250 mg/kg fresh wt.). They are also present in red wine (up to 300 mg/L), but green tea and chocolate are by far the good sources. An infusion of green tea contains up to 200 mg catechins (Lakenbrink *et al.,* 2000). Black tea contains fewer monomer flavanols, which are oxidized during "fermentation" (heating) of tea leaves to more complex condensed forms as the aflavins (dimers) and the arubigins (polymers). Catechin and epicatechin are the main flavanols in fruits, whereas gallocatechin, epigallocatechin and epigallocatechingallate are found in certain seeds of leguminous plants and more importantly in tea (Arts *et al.,* 2000). In contrast to other classes of flavonoids, flavanols are not glycosylated in foods. The tea epicatechins are remarkably stable when exposed to heat as long as the pH is acidic (Zhu *et al.,* 1997). Proanthocyanidins, which are also known as condensed tannins are dimers, oligomers and polymers of catechins that are bound together by links between C4 and C8 (or C6). In cider apples, the mean degree of polymerization ranges from 4 to 11 (Guyot *et al.,* 1998). Through the formation of complexes with salivary proteins, condensed tannins are responsible for the astringent character of fruits (grapes, peaches, kakis, apples, pears, berries, etc) and beverages (wine, cider, tea, beer, etc.) and for the bitterness of chocolate (Santos-Buelga *et al.,* 2000). This astringency changes over the course of maturation and often disappears when the fruit reaches ripeness. Such polymerization of tannins probably accounts for the apparent reduction in tannin content that is commonly seen during the ripening of many types of fruits. Anthocyanins are pigments dissolved in the vacuolar sap of the epidermal tissues of flowers and fruits, to which they impart a pink, red, blue, or purple color. They exist in different chemical forms, both colored and uncolored according to pH. Although they are highly unstable in the aglycone form (anthocyanidins), yet in plants, they are resistant to light, pH and oxidation conditions those 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. In addition, anthocyanins are stabilized by the formation of complexes with other flavonoids (co-pigmentation). In the human diet, anthocyanins are found in red wine, certain varieties of cereals, certain leafy and root vegetables (aubergines, cabbage, beans, onions, radishes), but they are most abundant in fruits. Cyanidin is the most common anthocyanidin in foods. Food contents are generally proportional to color intensity and reach values up to 2–4 g/kg fresh weight in black currants or black berries. The amount increases as the fruit ripens. 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). Wine contains 200–350 mg of anthocyanins/L, and these anthocyanins are transformed into various complex structures as the wine ages (Clifford, 2000).

2.3 Stilbenes

Stilbenes contain two phenyl moieties connected by a two-carbon methylene bridge. Stilbenes exist as stereo-isomers and naturally occurring stilbenes are present in the Transform. They occur in free and glycosylated forms and as dimeric, trimeric and polymeric stilbenes, the so-called viniferins (Rijke *et al.,* 2006). Occurrence of stilbenes in the human diet is quite low. It is produced by plants in response to infection by pathogens or to a variety of stress conditions. Most stilbenes in plants act as anti-fungal phytoalexins and some act as anti-carcinogenic. It has been detected in more than 70 plant species including grapes, berries and peanuts (Saleem *et al.,* 2005).

2.4 Lignans

Lignans are diphenolic compounds that contain a 2, 3-dibenzylbutane structure which 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 (Bertelli *et al.,* 1998). Lignans are metabolized to enterodiol and enterolactone by the intestinal microflora. The low quantities of secoisolariciresinol and matairesinol that are ingested as part of our normal diet do not account for the concentrations of the metabolites enterodiol and enterolactone that are classically measured in plasma and urine. Thus, there are undoubtedly other lignans of plant origin that are precursors of enterodiol and enterolactone and that have not yet been identified (Adlercreutz *et al.,* 1997).

3. Polyphenols and Human Diseases

Polyphenols have a great role in reducing the risk of chronic human diseases. It is well established that polyphenol-rich foods and beverages may increase plasma anti-oxidant capacity. This increase in the anti-oxidative capacity of plasma following the consumption of polyphenol-rich food may be explained either by the presence of reducing polyphenols or 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, such as iron (Scalbert, 2005). Consumption of antioxidants has been associated with reduced levels of oxidative damage to lymphocytic DNA. Similar, observations have been made with polyphenol rich food and beverages indicating the protective effects of polyphenols (Arts *et al.,* 2005). The structural modulation/modification of polyphenol compounds could provide potent inhibitors against bacterial pathogens such as *Streptococcus mutans* and *Mycobacterium tuberculosis* (Ahmad *et al.,* 2012). There are increasing evidences that as antioxidants, polyphenols may protect cell constituents against oxidative damage and therefore, limit the risk of various degenerative diseases associated with oxidative stress (Cliforrd, 2000; Vitrac *et al.,* 2002). Stockmham *et al.* (2013) investigated that polyphenolic compounds in wine affected by climate, CO_2 level and region. The warmer climate lowers the antioxidant capacity value but retained good bio-availability. Ferrazzano *et al.* (2009) found that polyphenols occurring in cocoa, coffee and tea have major role in prevention of cariogenic processes due to their antibacterial action. Cocoa polyphenol pentamers significantly reduces biofilm formation and acid production by *S. mutans and S. sanguinis*. Tea polyphenols exert an anti-caries effect via antimicrobial mode of action and galoyl esters of epicatechin, epigallocatechin and gallocatechin show increased anti-bacterial activity. Tea polyphenols also exhibit an anti-depressant activity which may relate to the alteration of monoaminergic response and anti-oxidant defenses (Nam *et al.,* 2001; Kim *et al.,* 2013). Polyphenols have been found to be the promising agents towards cervical cancer by induction of apoptosis, growth arrest and inhibition of DNA synthesis and modulation of signal transduction pathways. They can interfere with each stage of carcinogenesis, initiation, promotion and progression to prevent cancer development (Sabu *et al.,* 2001; Domenico *et al.,* 2012).

4. Cardio-Protective Effect

Cardiovascular disease (CVD) risks include urinary isoprostanes, LDL oxidation, endothelial function, platelet aggregation, and inflammatory status (Scalbert *et al.,* 2005; Quiñones *et al.,* 2013). Consumption of polyphenols limits the incidence of coronary heart diseases. Atherosclerosis is a chronic inflammatory disease that develops in lesion-prone regions of medium-sized arteries that leads to acute myocardial infarction, unstable angina or sudden cardiac death (Vita, 2005). Polyphenols are potent inhibitors of LDL oxidation and this type of oxidation is considered to be a key mechanism in development of atherosclerosis (Aviram *et al.,* 2000). Other mechanisms by which polyphenols may be protective against CVDs are antioxidant, anti-platelet, anti-inflammatory effects as well as increasing HDL and improving endothelial function (Wang *et al.,* 2006; Garcia-lafuente *et al.,* 2009). Polyphenols may also contribute to stabilization of the atheroma plaque. Quercetin, the abundant polyphenol in onion inhibits the expression of metalloproteinase 1 (MMP1) and the disruption of atherosclerotic plaques that leads to CVDs. Tea catechins have been shown to inhibit the invasion and proliferation of the smooth muscle cells in the arterial wall, a mechanism that may contribute to slow down the formation of the atheromatous lesion (Maeda *et al.,* 2003). Consumption of red wine or non-alcoholic wine reduces bleeding time and platelet aggregation (Naveena *et al.,* 2008). Polyphenols can improve endothelial dysfunction associated with different risk factors for atherosclerosis before the formation of plaque, its use as a prognostic tool for coronary heart diseases has also been proposed (Schachinger *et al.,* 2002). Tea polyphenols increase the artery dilation, improve endothelial dysfunction or estrogen like activity (Duffy *et al.,* 2001) and lowers the blood pressure. Resveratrol inhibits the inducer of the platelet aggregation and vasoconstrictor (Hari kumar and Aggarwal, 2008). In addition to this, resveratrol is capable of relaxing the isolated arteries and rat aortic rings. The ability to stimulate Ca^{++} activated K^+ channels and to enhance nitric oxide signaling in the endothelium are other pathways by which resveratrol exerts vasorelaxant activity (Cucciolla *et al.,* 2007; Shakibaei *et al.,* 2009). Direct relation between CVDs and oxidation of LDL is now well established. Oxidation of LDL particles is strongly associated with the risk of coronary heart diseases and myocardial infarctions. Gorinstein *et al.* (2002) have found that the intake of phenol rich virgin olive oil decreases TC, LDL-C and triglyceride levels and substantially increases (HDL-C concentrations) in rats. Resveratrol is the active compound in red wine which is attributed for “French Paradox” the low incidence of CVD despite the intake of high-fat diet and smoking among French (Peters, 2001; Yang, 2001). Association between polyphenol intake or the consumption of polyphenol-rich foods and CVDs were also examined in several epidemiological studies and it was found that consumption of polyphenol rich diet have been associated with a lower risk of myocardial infarction in both case-control and cohort studies (Xia *et al.,* 2010).

5. Anti-Cancer Effect

Plant polyphenols form one of the most important and extensively used classes of plant-derived therapeutics for cancer prevention and chemotherapy. Polyphenols induce a reduction of the number of tumors or of their growth, results in protective effect (Galleano *et al.,* 2010; Martins *et al.*, 2011) at various sites including mouth, stomach, duodenum, colon, liver, lung, mammary gland or skin. Many polyphenols such as quercetin, catechins, isoflavones, lignans, flavanones, ellagic acid, red wine polyphenols, resveratrol and curcumin have been tested and all of them showed protective effects (Scalbert, 2005). Pastrana *et al.* (2003) studied that the epigallocatechingallate in green tea has cancer preventive effect. Several mechanisms of action have been identified for chemoprevention effect of polyphenols, such as plant polyphenols can act as antioxidants, reducing free radicals and ROS thus decreasing their damaging effects on DNA. The expression of enzyme cytochrome P450 involved in activation of carcinogens and polyphenols act as modulator in their action. They may also facilitate their excretion by increasing the expression of phase II conjugating enzymes. This induction of phase II enzymes may have its origin in the toxicity of polyphenols (Khan and Mukhtar, 2008). Polyphenols can form potentially toxic quinones in the body that are themselves, substrates of these enzymes. The intake of polyphenols could then activate these enzymes for their own detoxification and thus, induce a general boosting of our defenses against toxic xenobiotics (Sharma and Rao, 2009). It has been demonstrated that tea catechins in the form of capsules when given to men with high-grade prostate intraepithelial neoplasia (PIN) demonstrated cancer preventive activity. Black tea polyphenols were found to inhibit proliferation and increase apoptosis in Du 145 prostate carcinoma cells. Higher level of insulin like growth factor-1 (IGF-1) was found to be associated with a higher risk of development of prostate cancer. IGF-1 binding to its receptor is a part of signal transduction pathway which causes cell proliferation (Kamaraj *et al.,* 2007). Black tea polyphenol addition was found to block IGF-1 induced progression of cells into S phase of cell cycle at a dose of 40 mg/ml in prostate carcinoma cells (Athar *et al.,* 2007). Quercetin has also been reported to possess anti-cancer property against benzopyrene induced lung carcinogenesis in mice, an effect attributed due to its free radical scavenging activity (Rizvi and Zaid, 2001). Resveratrol prevents all stages of development of cancer and has been found to be effective in most types of cancer including lung, skin, breast, prostate, gastric and colorectal cancer. It has also been shown to suppress angiogenesis and metastasis. Extensive data in human cell cultures indicate that resveratrol can modulate multiple pathways involved in cell growth, apoptosis and inflammation.

6. Anti-Diabetic Effect

Impairment in glucose metabolism leads to physiological imbalance with the onset of the hyperglycemia and sub-sequently diabetes mellitus. There are two main categories of diabetes: type-1 and type-2. Studies have shown that several physiological parameters of the body get altered in the diabetic conditions (Rizvi and Zaid, 2001; Rizvi *et al.*, 2005). Long term effects of diabetes include progressive development of specific complements such as retinopathy, which lead to blindness, nephropathy in which the renal functions are altered or disturbed and neuropathy which is associated with the risks of amputations, foot ulcers and features of autonomic disturbance including sexual dysfunctions. Numerous studies report the antidiabetic effects of polyphenols especially tea catechins (Matsui *et al.,* 2002). The active catechin green tea has anti-diabetic effect (Peng *et al.,* 2005). Polyphenols may affect glycemia through different mechanisms, including the inhibition of glucose absorption in the gut or of its uptake by peripheral tissues. The hypoglycemic effects of diacetylatedanthocyanins at 10 mg/kg diet dosage were observed with maltose as a glucose source, but not with sucrose or glucose (Matsui *et al.,* 2001). This suggests that these effects are due to an inhibition of α-glucosidase in the gut mucosa. Inhibition of α-amylase and sucrase in rats by catechin at a dose of about 50 mg/kg diet or higher was also observed. The inhibition of intestinal glycosidases and glucose transporter by polyphenols has been studied (Dembinska-Kiec *et al.,* 2008). Individual polyphenols such as (+) catechin, (-) epicatechin, (-) epigallocatechin, epicatechingallate, isoflavones from soyabeans, tannic acid, glycyrrhizin from licorice root, chlorogenic acid and saponins also decrease S-Glut-1 mediated intestinal transport of glucose. Saponins additionally delay the transfer of glucose from stomach to the small intestine (Hari kumar and Aggarwal, 2008). Resveratrol has also been reported to act as an anti-diabetic agent. Many mechanisms have been proposed to explain the anti-diabetic action of this stilbene (Dudonné *et al.,* 2009). The grape seed polyphenols inhibit high glucose induced cytotoxicity and oxidative stress. Resveratrol inhibits diabetes-induced changes in the kidney (diabetic nephropathy) and significantly ameliorates renal dysfunction and oxidative stress in diabetic rats. It also decreases insulin secretion and delayed the on set of insulin resistance due to inhibition of K^+ ATP and K^+ channel in β cells (Chen *et al.,* 2007).

Quercetin from onion significantly protects the lipid peroxidation and inhibits anti-oxidant system in diabetics (Rizvi and Mishra, 2009). Ferulic acid (FA) is another polyphenol very abundant in vegetables and maize bran. Several lines of evidence have shown that FA acts as a potent anti-diabetic agent by acting at many levels. It was demonstrated that FA lowered blood glucose followed by significantly increased plasma insulin and a negative co-relation between blood glucose and plasma insulin was observed (Scalbert *et al*., 2005; Barone *et al.*, 2009).

7. Anti-Aging Effect

Aging is the accumulation process of diverse detrimental changes in the cells and tissues with advancing age that occur due to free radical/oxidative changes resulting in an increase in the risks of disease and death. A certain amount of oxidative damage takes place even under normal conditions. However, the rate of this damage increases during the aging process as the efficiency of anti-oxidative and repair mechanisms decreases (Rizvi and Maurya, 2007). It has been found that the intake of anti-oxidant rich diet that is polyphenolic diet is effective in reducing the deleterious effects of aging and behavior. Anthocyanins are responsible for colors in fruits, and they have been shown to have potent anti-oxidant/anti-inflammatory activities, as well as to inhibit lipid peroxidation and the inflammatory mediators cyclo-oxygenase (COX)-1 and (COX)-2 (Seeram *et al.*, 2003). A recent study demonstrates that the tea catechins carry strong anti-aging activity and consuming green-tea rich in these catechins, may delay the onset of aging (Maurya and Rizvi, 2008). Polyphenols are also beneficial in ameliorating the adverse effects of the aging on nervous system or brain. Paramount importance for the relevance of food polyphenols in the protection of the aging brain is the ability of these compounds to cross the blood-brain barrier (BBB), which tightly controls the influx in the brain of metabolites and nutrients as well as of drugs. Resveratrol has been found to consistently prolong the life span, its action is linked to an event called caloric restriction or partial food deprivation (Hari kumar and Aggarwal, 2008). Grape polyphenols, resveratrol is very recent entry as an anti-aging agent. It has been shown that the early target of the resveratrol is the sirtuin class of nicotinamide adenine dinucleotide dependent deacetylases. Seven sirtuins have been identified in mammals, of which SIRT-1 is believed to mediate the beneficial effects on health and longevity of both caloric restriction and resveratrol (Markus and Morris, 2008). Resveratrol increased insulin sensitivity, decreased the expression of IGF-1 and increased AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-c coactivator 1a (PGC-1a) activity. When examined for the mechanism, it activated forkhead box O, which regulates the expression of genes that contribute both longevity and resistance to various stresses and insulin-like growth factor binding protein 1 (Barger *et al.*, 2008). There are experimental evidences that resveratrol can extend life span in the yeast *Saccharomyces cerevisiae*, the fruit fly *Drosophila melanogaster*, the nematode worm *C. elegans* and seasonal fish *Nothobranchius furzeri* (Shakibaei *et al.*, 2009). Recently quercetin has also been reported to exert preventive effect against aging (Belinha *et al.*, 2007).

8. Neuro-Protective Effects

Oxidative stress and damage to brain macromolecules is an important process in neuro-degenerative diseases. Alzheimer’s disease is one of the most common occurring neuro-disorder affecting up to 18 million people worldwide. Because polyphenols are highly anti-oxidative in nature, their consumption may provide protection in neurological diseases (Letenneur *et al.*, 2007). It was observed that the people drinking three to four glasses of wine per day had 80% decreased incidence of dementia and Alzheimer’s disease compared to those who drank less or did not drink at all (Scarmeas *et al.*, 2007). Resveratrol, abundantly present in wine scavenges O_2 and OH *in vitro*, as well as lipid hydroperoxyl free radicals; this efficient anti-oxidant activity is probably involved in the beneficial effect of the moderate consumption of red wine against dementia in the elderly. It was found that the consumption of fruit and vegetable juices containing high concentrations of polyphenols, at least three times per week, may play an important role in delaying the onset of Alzheimer’s disease (Dai *et al.*, 2006). Polyphenols from fruits and vegetables seem to be invaluable potential agents in neuro-protection by virtue of their ability to influence and modulate several cellular processes such as signaling, proliferation, apoptosis, redox balance and differentiation (Singh *et al.*, 2008). Recently Aquilano *et al.* (2008) reported that administration of polyphenols provide protective effects against Parkinson’s disease, a neuro-logical disorder characterized by degeneration of paminergic neurons in the substantia nigra zona compacta of brain. Nutritional studies have linked the consumption of green tea to the reduced risk of developing Parkinson’s disease. In animal, epigallocatechingallate (EGCG) has been shown to exert a protective role against the neurotoxin MPTP (N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), an inducer of a Parkinson’s like disease, either by competitively inhibiting the uptake of the drug by scavenging MPTP mediated radical formation. EGCG may also protect neurons by activating several signaling pathways, involving MAP kinases which are fundamental for cell survival (Rossi *et al.,* 2008). The therapeutic role of catechins in Parkinson's disease is also due to their ability to chelate iron. This property contributes to their anti-oxidant activity by preventing redox-active transition metal from catalyzing free radicals formation. Moreover, the antioxidant function is also related to the induction of the expression of anti-oxidant and detoxifying enzymes particularly in the brain, which is not sufficiently endowed of a well-organized anti-oxidant defense system (Aquilano *et al.*, 2008). Maize bran polyphenol, ferulic acid is also reported to be beneficial in Alzheimer's disease. This effect is due to its antioxidant and anti-inflammatory properties (Barone *et al.*, 2009).

Others

Except above explained pathological events, polyphenols show several other health beneficial effects. Dietary polyphenols exert preventive effects in treatment of asthma. In asthma, the airways react by narrowing or obstructing when they become irritated. This makes it difficult for the air to move in and out. This narrowing or obstruction can cause one or a combination of symptoms such as wheezing, coughing, shortness of breath and chest tightness. Epidemiological evidence shows that polyphenols might protect against obstructive lung disease come from studies that have reported negative associations of apple intake with prevalence and incidence of asthma, and a positive association with lung function (Tabak *et al.,* 2001; Woods *et al.,* 2003). Increased consumption of the soy iso-flavone, genistein was associated with better lung function in asthmatic patients (Smith *et al.,* 2004). Intake of polyphenols is also reported as beneficial in osteoporosis. Supplementation of diet with genistein, daidzein or their glycosides for several weeks prevent the loss of bone mineral density and trabecular volume caused by the ovariectomy (Nakajima *et al.*, 2001). Polyphenols also protect skin damages induced from sunlight. Study on animals provide evidence that polyphenols present in the tea, when applied orally or topically, ameliorate adverse skin reactions following UV exposure, including skin damage, erythema and lipid peroxidation (Kim *et al.*, 2001). Black tea polyphenols are reported to be helpful in mineral absorption in intestine as well as to possess antiviral activity.The aflavins present in black tea were found to have anti HIV-1 activity. These polyphenols inhibited the entry of HIV-1 cells into the target cells (Sharma and Rao, 2009).

Conclusion

Phenolic compounds are a much diversified group of phytochemicals that are widely distributed in plants such as fruits, vegetables, tea, olive oil, tobacco and so on. Now a days, there is a growing interest in substances exhibiting anti-oxidant properties, which are supplied to human organisms as food components or as specific preventive pharmaceuticals. Consequently, anti-oxidants have become an essential part of preservation technology and contemporary health care. It is well known that plants which possess anti-oxidative and pharmacological properties are related to the presence of phenolic compounds, especially phenolic acids and flavonoids.

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