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POLYPHENOLS AND HUMAN HEALTH- A REVIEW

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ABSTRACT

Flavonoids, perhaps the most important single group of phenolics in foods, comprise a group of over 4000 C_{15} aromatic plant compounds with multiple substitution patterns. Anthocyanins are members of the flavonoid group of phytochemicals, a group predominant in teas, wines, fruits, vegetables, nuts, olive oil, cocoa, and cereals. The colorful anthocyanins are the most recognized, visible members of the bioflavonoid phytochemicals with proven human health benefits of myriad nature. Anthocyanin isolates and anthocyanin-rich mixtures of bioflavonoids provide protection from DNA cleavage, estrogenic activity, enzyme inhibition, boosting production of cytokines, anti-inflammatory activity, lipid peroxidation, decreasing capillary permeability and fragility, and membrane strengthening. To add to the importance of anthocyanin pigments in human health, both in vitro and in vivo research trials have amply demonstrated their marked ability to reduce cancer cell proliferation and to inhibit tumor formation. The capacity of anthocyanin pigments to interfere with the process of carcinogenesis seems to be linked to multiple potential mechanisms of action including inhibition of cyclooxygenase enzymes and potent antioxidant potential. Another feather in cap is the role of anthocyanins in cardiovascular disease protection which is strongly linked to oxidative stress protection.

KEYWORDS: **Anthocyanins, flavonoids, free radical scavengers, anti-oxidants**

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1. INTRODUCTION

Herbs, vegetables and fruits have been used in many domains including medicine, nutrition, flavoring, beverages, dyeing, repellents, fragrances, cosmetics and other industrial purposes. Since, the pre-historic era, these plants have been the basis for nearly all medicinal therapy and synthetic drug usage (Dahamuka et al., 2000). The medicinal value of these plants is related to their phytochemical components which produce definite physiological actions on human body. The most important of these components are alkaloids, tannins, flavonoids and phenolic compounds. Several herbs have been reported to exhibit antioxidant activity and a great potential source of antioxidant are polyphenols (Mohammedi and Atik, 2011). The benefit of these plants is related to the secondary metabolites that are produced by the plants even though plants produced these secondary metabolites for the benefits of the plant itself as defense against infection and injury, but it was found that the secondary metabolites have benefits to the human health and curing human diseases. The preservative effect of many vegetables, fruits, spices and herbs suggest the presence of anti-oxidative and anti-microbial constituents in their tissues (Hirasa and Jackson). Interest has considerably increased in finding naturally occurring anti-oxidants for use in foods or medicinal materials to replace synthetic anti-oxidants, which are having restrictions due to their carcinogenicity. Fruits contain large amounts of anti-oxidants such as polyphenols and anthocyanins which can play an important role in adsorbing and neutralizing free radicals or decomposing peroxides (Anderson et al., 2002).

The importance of the anti-oxidant constituents of plant materials in the maintenance of health and protection from coronary heart disease and cancer is also raising interest among scientists, food manufacturers and consumers as the trend of the future is moving toward functional foods with specific health effects (Loliger, 1991). Phenolic compounds have proved useful as makers of strawberry cultivars (Meyer et al., 2003; Simirgiotis et al., 2010), processing types (Oszmianski and Wojdylo, 2009; Hartmann et al., 2008;) and day/night growing temperature (Wang and Zheng 2001). The major phenolic compounds are procyanidins (137-179 mg/kg of fresh weight), cyonidins (24-90 mg/kg of fresh weight), and p-coumaroyl esters (23 mg/kg of fresh weight) (Aaby et al., 2005; Matta Rihinen et al., 2004). It is well known that pelargonidin-3-glucoside is the major anthocynanin in strawberry (15-652mg/kg of fresh weight) (Gracia Vignera et al., 2007). Strawberry fruits have been shown to possess high in-vitro anti-oxidant activity that has been positively correlated with the content of polyphenolic compounds and specially anthocynanins, the type of polyphenols quantitatively most important in strawberry (Heinonen,et al, 1998; Wang and Jiao, 2000; Wang and Lin, 2000). Strawberry anthocynanins derive from pelargonidin (Pg) and cyanidin (Cy) aglycones. Anthocynanins belong to the flavanoid group and are responsible for the bright red color of strawberry fruits. Despite a great number of anthocynanins being identified in strawberry fruit, pelargonidin -3- glucoside, pelargonidin- 3-rutinoside, and cyanidin-3-glucoside represents over 95% of the total anthocyanin bulk in most strawberry fruits (Lopes et al., 2007).

Assessment of strawberry quality of the market is focused on visual and internal characteristics such as size, color, firmness, aroma, sweetness and acidity (Azondanlou et al., 2003; Mitcham, 2004), but there is an increasing interest in the health benefits of the fruit. Beneficial effects of strawberry include increased plasma anti-oxidants capacity in humans (Cao et al., 1998), anti-oxidant activity for low density lipo-proteins (Heinonen et al., 1998) and anti carcinogenic activity against human and mouse cancer cells (Smith et al., 2004; Wang et al., 2005). Strawberry fruit has high ascorbic acid concentrations which have protective roles against Reactive oxygen species (Davey et al., 2000) but it has become increasingly clear that many other components within the fruit also have anti-oxidant activity. Reactive oxygen species (ROS) for example Superoxide anion (O^{2-}), singlet O_2, hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), hydroxyl radical (OH), peroxynitrite ($OONO^-$) and peroxy and alloxy radicals can cause cell damage at various sites such as membranes, cytoplasm and nucleus; leading to several human diseases such as diabetes, arteriosclerosis, cardio- vascular illness, cancer, several neurodegenerative disorders and the aging process, Antioxidants are both natural and artificial (synthetic) compounds which are capable to scavenge free radical or ROS and to inhibit oxidation processes. Epidemiological studies and intervention trials on prevention of cancer and cardio-vascular diseases in people taking anti-oxidant supplements are suggestive that dietary intake of anti-oxidant can help scavenge free radicals and oxidants and protect the body against diseases. However, artificial anti oxidants such as Butylated hydroxyanisole (BHA), Butylated hydroxyl toluene (BHT) and tertiary butyl hydroquinone (TBHQ) that have been widely used for preventing lipid per oxidation in several food products are gradually limited and controlled by the food industry because they are suspected to be toxic and carcinogenic (Namiki,1990).

Flavanoids and other phenolics have been suggested to play a preventive role in the development of cancer and heart diseases. Consumption of controlled diet rich in fruits and vegetables increased significantly the antioxidants capacity of plasma and the increase could not be explained by the increase in the plasma alpha- tocopherol carotenoid concentrations (Cao et al, 1998). Moreover epidemiological studies have found that there is a significant negative association between the intake of fruits and vegetables and heart disease mortality (Hertog et al., 1993, Knekt et al., 1995). Polyphenolic compounds, widely distributed in higher plants have been found to have potential health benefits that are believed to arise mainly from their anti-oxidant activity. There is considerable scientific and public interest in the important role that anti-oxidant may play in health care, such as by acting as cancer chemo preventive and anti-inflammatory agents and by reducing the risk of cardiovascular mortality (Cos et al., 2004). Rai Hui Lui (2003) found that health benefits of fruit and vegetables are from additive and synergistic combinations of phytochemicals. The anti-oxidant activity of phenolics is mainly due to their redox properties, which allow them to act as reducing agents, hydrogen donators and singlet oxygen quenchers. In addition they have metal chelation properties (Rice-Evans et al., 1995). Berries and fruits contain a wide range of flavonoids and phenolic acids that show anti-oxidant activity. Main flavanoid sub groups in berries and fruits are anthocyanins, proanthocyanins, flavonols and catechins. Phenolic acids present in berries and fruits are hydroxylated derivatives of benzoic acid and cinnamic acid (Macheix et al., 1990). Studies on anti-oxidative activities of fruit extracts have been focused mainly on grapes, which have been reported to inhibit oxidation of human low density lipoprotein (LDL) at a level comparable to wine (Meyer et al., 1997). Fresh strawberry extract was reported to have 15 times higher total anti-oxidant capacity than trolox in an artificial peroxyl radical model system (Wang et al., 1997).

2. Anti-oxidants in fruits

Fruits contain large amounts of anti-oxidants such as polyphenols and anthocyanins, which can play an important role in absorbing and neutralising free radicals or decomposing peroxides (Anderson et al, 2002). Free radicals are atoms, molecules or ions with unpaired electrons in the outer shell and are chemically highly reactive. They can start a chain reaction which leads to oxidative stress. Oxidative stress is a situation where in pro-oxidants dominates over anti-oxidants. Pro-oxidants are the compounds that oxidize other cellular molecules resulting in mutations, loss of enzyme activity etc., it leads to various diseases, Alzheimers disease and muscular degeneration. Plant foods particularly, fruits are a rich source of anti-oxidants like vitamin E, vitamin C, carotenoid, polyphenols, anthocyanins, etc. The importance of the anti-oxidant constituents of plant materials in the maintenance of health and protection from cononary among scientists, food manufactures and consumers as the trend of future is moving towards functional foods a specific health effects (Lo-Liger, 1991). Berries and fruits contain a wide range of flavonoids and phenolic acids that show anti-oxidants activity. The main flavonoid sub-groups in berries and fruits are anthocyanins, pro-anthocyanins, flavonols and catechin. Phenolic acids present in berries and fruits are hydroxylated derivatives of benzoic acid and cinnamic acid (Macheix et al., 1990). The garden strawberry belongs to the subfamily Rosoideae of the Rosaceae family. Rosaideae species, particularly those belonging to the genera Rosa, Rubus and Fragaria are known to contain versatile secondary metabolites being especially rich in elagitannins. Because of the versatile elagitannin composition of plants of rosaceae family are interesting also for plants from the medicinal point of view. In addition elagitannins have shown anti-oxidative (Mullen et al., 2002) and anti-carcinogenic (seeram et al., 2007) activities. Strawberry is the most widely cultivated member of the Rosoideae and fairly extensive information is available on the chemical composition of its fruit (Aaby et al., 2007, Maattaa–Riihinen et al., 2004 and Aharoni et al, 2002).

Demand for and availability of strawberry have increased substantially during recent years driven in past by the highly derived taste of the fruit along with its known health promoting properties (Wang et al., 2005). Strawberry is known as non climacteric fruit of frequent human consumption (Avigdori-Avidov, 1986). Besides its attractive color and taste, strawberry is also a good source of vitamin C and other anti-oxidant compounds, such as flavanoids and ellagic acid (Robards et al., 1999). The main flavanoids present in strawberries are anthocyanins, which are responsible for its attractive color of the fruit, besides being very important for the evaluation of fruit ripeness. Ellagic acid is a polyphenol found in and berries such as strawberry, raspberry and blackberry (Tomas and Clifford, 2000). This compound can exist as free form glycoside or linked with ellagi-tannins esterified with glucose (Bate and smith 1972, Haddocla et al, 1982) although the free form of this compound is rarely found in strawberry represents the main source of ellagic acid derivaties in the Brazilian diet corresponding to more than 50% of all phenolic compounds found in the fruit (Hakkinen et al., 2000). Strawberries and red raspberries were rich in nutrients such as anthocyanins, amino acids and vitamins (Souci et al., 2000) but are highly perishable and have high physiolgical post harvest activities. As a consequence they have short repemary and senescent periods that make marketing a challenge (Gracia et al., 1998). Their storage life is terminated by the fungal infection (Ghaouth et al, 1991).

The major flavonoids in strawberry fruits have been described as the 3-glucoside of pelargonidin, cyanindin (anthocyanins), kaempferol and quercetin (flavonols), catechin (flavonol), and leucocyanidins of different degrees of poloymerisation (Cao and Markakis, 1968) and references here in addition to pelargonidin 3, 6 malonylglucoside and 3-rutinoside of cyandin and pelargonidin (Tamura et al., 1995; Bridle and Graciea-Viquera, 1997; Lopes de Silva et al 2002). From the roots of strawberry, +-taxifolin 3-0-Larabino furanoside a hydrlysable tannins (+) afzelechin (4-8) (+)-catechin, procyanidin B-3 and procycandin B-6, have been isolated (Ishimare et al, 1995). Recently, 5-carboxypyrano pelargonidin 3-glucoside has been isolated in small amounts from acidified methanol extracts of strawberries (Andersen et al., 2004). Strawberries have found to inhibit oesophageal cancer and to reverse the course of neuronal and behavioural aging in rats (Joseph et al., 2000 Torronen and Maatta, 2002). The anti-oxidant activity of strawberries in vitro oxidation content of fruits (Heinon et al., 1998; Hoang and Lin, 2000). It has been recently reported that strawberry proanthocyanidins may act both as anti fungal compounds to extend shelf life and as anti-oxidants to enhance quality preservation.

3. Polyphenols

Polyphenols are naturally occurring compounds found largely in the fruits, vegetables, cereals and beverages. Fruits like grapes, apple, pear, cherries and berries contains up to 200–300 mg polyphenols per 100 grams fresh weight. The products manufactured from these fruits, also contain polyphenols in significant amounts. Typically a glass of red wine or a cup of tea or coffee contains about 100 mg polyphenols. Cereals, dry legumes and chocolate also contribute to the polyphenolic intake (Scalbert et al., 2005 and Spencer et al., 2008) Polyphenols are secondary metabolites of plants and are generally involved in defense against ultraviolet radiation or aggression by pathogens. (Bechman et al, 2000). In food, polyphenols may contribute to the bitterness, astringency, color, flavor, odor and oxidative stability. Towards the end of 20th century, epidemiological studies and associated meta-analyses strongly suggested that long term consumption of diets rich in plant polyphenols offered some protection against development of cancers, cardiovascular diseases, diabetes, osteoporosis and neurodegenerative diseases (Graf et al., 2005) Polyphenols and other food phenolics are the subject of increasing scientific interest because of their possible beneficial effects on human health.

3.1 Classes of Polyphenols

More than 8,000 polyphenolic compounds have been identified in various plant species. All plant phenolic compounds arise from a common intermediate, 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 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. The main classes include phenolic acids, flavonoids, stilbenes and lignans (Spencer et al., 2008).

3.1.1 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, with the exception of certain red fruits, black radish and onions, which can have concentrations of several tens of milligrams per kilogram fresh weight (Shahidi and Naczk,1995). The hydroxycinnamic acids are more common than hydroxybenzoic acids and consist chiefly of p-coumaric, caffeic, ferulic and sinapic acids.

3.1.2 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. 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 (de Groot and Rauen, 1998). Based on the variation in the type of heterocycle involved, flavonoids may be divided into six subclasses: flavonols, flavones, flavanones, flavanols, anthocyanins and isoflavones. 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) Quercetin, myricetin, catechins etc., are some most common flavonoids. Chemical structures of sub-classes of flavonoids. Based on the variation in the type of heterocycle involved, flavonoids are divided into six major subclasses: flavonols, flavanones, flavanols, flavones, anthocyanins and isoflavones. Individual differences.

3.1.3 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. One of the best studied, naturally occurring polyphenol stilbene is resveratrol (3,4′,5-trihydroxystilbene), found largely in grapes. A product of grapes, red wine also contains significant amount of resveratrol.

3.1.4 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 (Adlercreutz. al1997).

3.2 Occurrence and Content

Distribution of phenolics in plants at the tissue, cellular and sub cellular levels is not uniform. Insoluble phenolics are found in cell walls, while soluble phenolics are present within the plant cell vacuoles. Certain polyphenols like quercetin are found in all plant products; fruit, vegetables, cereals, fruit juices, tea, wine, infusions etc., whereas flavanones and isoflavones are specific to particular foods. In most cases, foods contain complex mixtures of polyphenols. The outer layers of plants contain higher levels of phenolics than those located in their inner parts (Simon et al., 1992). Numerous factors affect the polyphenol content of plants, these include degree of ripeness at the time of harvest, environmental factors, processing and storage. Polyphenolic content of the foods are greatly affected by environmental factors as well as edaphic factors like soil type, sun exposure, rainfall etc. The degree of ripeness considerably affects the concentrations and proportions of various polyphenols (Manach et al., 2004). In general, it has been observed that phenolic acid content decreases during ripening, whereas anthocyanin concentrations increase. Many polyphenols, especially phenolic acids, are directly involved in the response of plants to different types of stress: they contribute to healing by lignifications of damaged areas possess antimicrobial properties, and their concentrations may increase after infection. (Parr and Bolwell, 2000).

Another factor that directly affects the polyphenol content of the foods is storage. Studies have proved that polyphenolic content of the foods change on storage, the reason is easy oxidation of these polyphenol (Manach et al., 2004). Oxidation reactions result in the formation of more or less polymerized substances, which lead to changes in the quality of foods, particularly in color and organoleptic characteristics. Such changes may be beneficial, as is the case with black tea or harmful as in browning of fruit. Storage of wheat flour results in marked loss of phenolic acids (Sosulki et al., 1982). After six months of storage, flour contained the same phenolic acids in qualitative terms, but their concentrations were 70% lower compared with fresh. Cold storage, in contrast, has slight effect on the content of polyphenols in apples, pears or onions (Price et al., 1997). Cooking also has a major effect on concentration of polyphenols. Onions and tomatoes lose between 75% and 80% of their initial quercetin content after boiling for 15 min, 65% after cooking in a microwave oven, and 30% after frying (Krozier et al., 1997).

3.3 Bioavailability of Polyphenols

Bioavailability is the proportion of the nutrient that is digested, absorbed and metabolized through normal pathways. Bioavailability of each and every polyphenol differs, however there is no relation between the quantity of polyphenols in food and their bioavailability in human body. Generally, aglycones can be absorbed from the small intestine; however most polyphenols are present in food in the form of esters, glycosides or polymers that cannot be absorbed in native form (D'Archivio et al., 2007). Before absorption, these compounds must be hydrolyzed by intestinal enzymes or by colonic microflora. During the course of the absorption, polyphenols undergo extensive modification; in fact they are conjugated in the intestinal cells and later in the liver by methylation, sulfation and/or glucuronidation (Day and Williamson, 2001). As a consequence, the forms reaching the blood and tissues are different from those present in food and it is very difficult to identify all the metabolites and to evaluate their biological activity (Setchell et al., 2003). Importantly it is the chemical structure of polyphenols and not its concentration that determines the rate and extent of absorption and the nature of the metabolites circulating in the plasma. The most common polyphenols in our diet are not necessarily those showing highest concentration of active metabolites in target tissues; consequently the biological properties of polyphenols greatly differ from one polyphenol to another. Evidence, although indirect, of their absorption through the gut barrier is given by the increase in the antioxidant capacity of the plasma after the consumption of polyphenols-rich foods (Duthie et al., 1999).

Polyphenols also differs in their site of absorption in humans. Some of the polyphenols are well absorbed in the gastro-intestinal tract while others in intestine or other part of the digestive tract. In foods, all flavonoids except flavanols exist in glycosylated forms. The fate of glycosides in the stomach is not clear yet. Most of the glycosides probably resist acid hydrolysis in the stomach and thus arrive intact in the intestine (Gee et al., 1998) where as, only aglycones and few glucosides can be absorbed. Experimental studies carried out in rats (Crepsy et al., 2002) showed that the absorption at gastric level is possible for some flavonoids, such as quercetin, but not for their glycosides. Moreover it has been recently shown that, in rats and mice, anthocyanins are absorbed from the stomach (D"Archivio et al., 2005). It was suggested that glucosides could be transported into enterocytes by the sodium dependent glucose transporter SGLT1, and then hydrolyzed by a cytosolic β-glucosidase. However the effect of glucosylation on absorption is less clear for isoflavones than for quercetin. (Manach et al., 2004). Proanthocyanidins differ from most of other plant polyphenols because of their polymeric nature and high molecular weight. This particular feature should limit their absorption through the gut barrier, and oligomers larger than trimers are unlikely to be absorbed in the small intestine in their native forms (Archivio et al., 2000).

It was observed that the hydroxycinnamic acids, when ingested in the free form, are rapidly absorbed by the small intestine and are conjugated as the flavonoids (Clifford, 2000). However these compounds are naturally esterified in plant products and esterification impairs their absorption because intestinal mucosa, liver and plasma do not possess esterases capable of hydrolyzing chlorogenic acid to release caffeic acid, and hydrolysis can be performed only by the microflora present in colon (Olthof et al., 2001). Though most of the poyphenols get absorbed in gastrointestinal tract and intestine but there are some poyphenols which are not absorbed in these locations. These polyphenols reach the colon, where microflora hydrolyze glycosides into aglycones and extensively metabolize these aglycones into various aromatic acids (Kuhnau, 1976). Aglycones are split by the opening of the heterocycle at different points depending on their chemical structure, and thus produce different acids that are further metabolized to derivatives of benzoic acid. After absorption, polyphenols go to several conjugation processes. These processes mainly include methylation, sulfation and glucuronidation, representing a metabolic detoxication process, common to many xenobiotics, that facilitates their biliary and urinary elimination by increasing their hydrophilicity. The methylation of poyphenols is also quite specific it generally occurs in the C3-position of the polyphenol, but it could occur in the C4′-position: in fact a notable amount of 4′-methylepigallocatechin has been detected in human plasma after tea ingestion (Lee et al., 2002). Enzymes like sulfo-transferases catalyze the transfer of a sulfate moiety during process of sulphonation. The sulfation occurs mainly in the liver, but the position of sulfation for polyphenols have not been clearly identified yet (Falany, 1997). Glucuronidation occurs in the intestine and in the liver, and the highest rate of conjugation is observed in the C3-position (Spencer et al., 1997). The conjugation mechanisms are highly efficient and free aglycones are generally either absent, or present in low concentrations in plasma after consumption of nutritional doses; an exception are green tea catechins, whose aglycones can constitute a significant proportion of the total amount in plasma (Hollman et al., 1997).

It is important to identify the circulating metabolites, including the nature and the positions of the conjugating groups on the polyphenol structure, because the positions can affect the biological properties of the conjugates. Polyphenol metabolites circulate in the blood bound to proteins; in particular albumin represents the primary protein responsible for the binding. Albumin plays an important role in bioavailability of polyphenols. The affinity of polyphenols for albumin varies according to their chemical structure (Dangles et al., 2001). Binding to albumin may have consequences for the rate of clearance of metabolites and for their delivery to cells and tissues. It is possible that the cellular uptake of metabolites is proportional to their unbound concentration. Finally, it is still unclear if the polyphenols have to be in the free form to exert their biological activity, or the albumin-bound polyphenols can exert some biological activity (D"Archivio et al., 2007).

Accumulation of polyphenols in the tissues is the most important phase of polyphenol metabolism because this is the concentration which is biologically active for exerting the effects of polyphenols. Studies have shown that the polyphenols are able to penetrate tissues, particularly those in which they are metabolized such as intestine and liver. Excretion of polyphenols with their derivatives occurs through urine and bile. It has been observed that the extensively conjugated metabolites are more likely to be eliminated in bile, whereas small conjugates, such as monosulfates, are preferentially excreted in urine. Amount of metabolites excreted in urine is roughly correlated with maximum plasma concentrations. Urinary excretion percentage is quite high for flavanones from citrus fruit and decreases from isoflavones to flavonols. Thus the health beneficial effects of the polyphenols depend upon both the intake and bioavailability (D"Archivio et al., 2007).

3.4 Polyphenols and Human Health

Epidemiological studies have repeatedly shown an inverse association between the risk of chronic human diseases and the consumption of S rich diet (Scalbert et al., 2005). The phenolic groups in polyphenols can accept an electron to form relatively stable phenoxyl radicals, thereby disrupting chain oxidation reactions in cellular components (Clifford, 2000). It is well established that polyphenol-rich foods and beverages may increase plasma antioxidant capacity. This increase in the antioxidative capacity of plasma following the consumption of polyphenol-rich food 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, such as iron (Scalbert et al., 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 (Vitrac et al., 2002). 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 (Luqman et al., 2009).

3.4.1 Cardio-Protective Effect

A number of studies have demonstrated that consumption of polyphenols limits the incidence of coronary heart diseases (Renaud et al., 2005). Atherosclerosis is a chronic inflammatory disease that develops in lesion-prone regions of medium-sized arteries. Atherosclerotic lesions may be present and clinically silent for decades before becoming active and producing pathological conditions such as 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., 2007). Other mechanisms by which polyphenols may be protective against cardiovascular diseases are antioxidant, anti-platelet, anti-inflammatory effects as well as increasing HDL, and improving endothelial function (García et al., 2009). Polyphenols may also contribute to stabilization of the atheroma plaque. Quercetin, the abundant polyphenol in onion has been shown to be inversely associated with mortality from coronary heart disease by inhibiting the expression of metalloproteinase 1 (MMP1), and the disruption of atherosclerotic plaques (García et al., 2009). 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). Polyphenols may also exert antithrombotic effects by means of inhibiting platelet aggregation. Consumption of red wine or non-alcoholic wine reduces bleeding time and platelet aggregation. Thrombosis induced by stenosis of coronary artery is inhibited when red wine or grape juice is administrated (Demrow et al., 1995). 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). It has been observed that consumption of black tea about 450 ml increases artery dilation 2 hours after intake and consumption of 240 mL red wine for 30 days countered the endothelial dysfunction induced by a high fat diet (Duffy et al., 2001). Long term regular intake of black tea was found to lower blood pressure in a cross-sectional study of 218 women above 70 years of age. Excretion of 4-O-methylgallic acid (4OMGA, a biomarker for tea polyphenols in body) was monitored. A higher consumption of tea and therefore higher excretion of 4OMGA were associated with lower blood pressure (BP). Tea polyphenols may be the components responsible for the lowering of BP. The effect may be due to antioxidant activity as well as improvement of endothelial function or estrogen like activity (García et al., 2009).

Resveratrol, the wine polyphenol prevents the platelet aggregation via preferential inhibition of cyclooxygenase 1(COX 1) activity, which synthesizes thromboxane A2, an inducer of the platelet aggregation and vasoconstrictor (Pirola L, and Frojdo S., 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 (Pirola et al., 2008).Direct relation between cardiovascular diseases (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. Studies have shown that resveratrol potentially inhibits the oxidation of the LDL particles via chelating copper or by direct scavenging of the free radicals. 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 (Cucciolla et al., 2009). The association between polyphenol intake or the consumption of polyphenol-rich foods and incident of cardiovascular diseases were also examined in several epidemiological studies and it was found that consumption of polyphenol rich diet have been associated to a lower risk of myocardial infarction in both case-control and cohort studies (Peters et al., 2001).

3.4.2 Anti-Cancer Effect

Effect of polyphenols on human cancer cell lines, is induces most often protective and a reduction of the number of tumors or of their growth (Yang et al., 2001). These effects have been observed 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; all of them showed protective effects in some models although their mechanisms of action were found to be different (ohnson et al., 1994). Development of cancer or carcinogenesis is a multistage and microevolutionary process. Into the three major stages of carcinogenesis: initiation, promotion and progression. Initiation is a heritable aberration of a cell. Cells so initiated can undergo transformation to malignancy if promotion and progression follow. Promotion, on the other hand, is affected by factors that do not alter DNA sequences and involves the selection and clonal expansion of initiated cells.

Several mechanisms of action have been identified for chemoprevention effect of polyphenols, these include estrogenic/ antiestrogenic activity, antiproliferation, induction of cell cycle arrest or apoptosis, prevention of oxidation, induction of detoxification enzymes, regulation of the host immune system, anti-inflammatory activity and changes in cellular signaling(García et al,.2009). Polyphenols influence the metabolism of pro-carcinogens by modulating the expression of cytochrome P450 enzymes involved in their activation to carcinogens. 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 (Scalbert et al., 2005). 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 detoxication and, thus, induce a general boosting of our defenses against toxic xenobiotics (Talalay et al., 1988). 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 by inhibiting the conversion of high grade PIN lesions to cancer (Khan N,and Mukhtar H.2008).

Theaflavins and thearubigins, the abundant polyphenols in black tea have also been shown to possess strong anticancer property. 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 .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 (Sharma and Rao, 2009). Quercetin has also been reported to possess anticancer property against benzo (a) pyrene induced lung carcinogenesis in mice, an effect attrtibuted to its free radical scavenging activity (Kamaraj et al., 2007). 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. The anti-carcinogenic effects of resveratrol appears to be closely associated with its antioxidant activity, and it has been shown to inhibit cyclooxygenase, hydroperoxidase, protein kinase C, Bcl-2 phosphorylation, Akt, focal adhesion kinase, NFκB, matrix metalloprotease-9 and cell cycle regulators (Athar et al., 2007). These and other in vitro and in vivo studies provide a rationale in support of the use of dietary polyphenols in human cancer chemoprevention, in a combinatorial approach with either chemotherapeutic drugs or cytotoxic factors for efficient treatment of drug refractory tumor cells.

3.4.3 Anti-Diabetic Effect

Impairment in glucose metabolism leads to physiological imbalance with the onset of the hyperglycemia and subsequently 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 et al., 2005). Long term effects of diabetes include progressive development of specific complements such as retinopathy, which affects the eyes and 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. Tea catechins have been investigated for their anti-diabetic potential(Rizvi et al., 2001). 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 diacetylated anthocyanins at a 10 mg/kg diet dosage were observed with maltose as a glucose source, but not with sucrose or glucose (Matsui et al., 2002).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 (Matsui et al., 2001). Individual polyphenols, such as (+)catechin, (−)epicatechin, (−)epigallocatechin, epicatechin gallate, 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 (Dembinska et al., 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, modulation of SIRT1 is one of them which improves whole-body glucose homeostasis and insulin sensitivity in diabetic rats (Harikumar et al., 2008).It is reported that in cultured LLC-PK1 cells, high glucose induced cytotoxicity and oxidative stress was inhibited by grape seed polyphenols. Resveratrol inhibits diabetes-induced changes in the kidney (diabetic nephropathy) and significantly ameliorates renal dysfunction and oxidative stress in diabetic rats. Treatment with resveratrol also decreased insulin secretion and delayed the onset of insulin resistance. A possible mechanism was thought to be related to the inhibition of K + ATP and K + V channel in beta cells (Chen et al., 2007).

Onion polyphenols, especially quercetin is known to possess strong anti diabetic activity. A recent study shows that quercetin has ability to protect the alterations in diabetic patients during oxidative stress. Quercetin significantly protected the lipid peroxidation and inhibition antioxidant system in diabetics (Rizvi and Mishra, 2009). *Hibiscus sabdariffa* extract contains polyphenolic acids, flavonoids, protocatechuic acid and anthocyanins. A study performed by Lee et al. (Lee et al., 2009). Showed that polyphenols present in the extracts from *Hibiscus sabdariffa* attenuate diabetic nephropathy including pathology, serum lipid profile and oxidative markers in kidney. 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 a significantly increased plasma insulin and a negative correlation between blood glucose and plasma insulin (Barone et al., 2007).

3.4.4 Anti-Aging Effect

Aging is the accumulation process of diverse detrimental changes in the cells and tissues with advancing age, resulting in an increase in the risks of disease and death. Among many theories purposed for the explaining the mechanism of aging, free radical/oxidative stress theory is one of the most accepted one (Harman, 2006). A certain amount of oxidative damage takes place even under normal conditions; however, the rate of this damage increase during the aging process as the efficiency of antioxidative and repair mechanisms decrease (Rizvi et al., 2007). Antioxidant capacity of the plasma is related to dietary intake of antioxidants; it has been found that the intake of antioxidant rich diet is effective in reducing the deleterious effects of aging and behavior. Several researches suggest that the combination of antioxidant/anti-inflammatory polyphenolic compounds found in fruits and vegetables may show efficacy as anti-aging compounds (Cao et al., 2005). Subset of the flavonoids known as anthocyanins, are particularly abundant in brightly colored fruits such as berry fruits and concord grapes and grape seeds. Anthocyanins are responsible for the colors in fruits, and they have been shown to have potent antioxidant/anti-inflammatory activities, as well as to inhibit lipid peroxidation and the inflammatory mediators cyclo-oxygenase (COX)-1 and -2 (Seeram et al., 2003).

Fruit and vegetable extracts that have high levels of flavonoids also display high total antioxidant activity such as spinach, strawberries and blueberries. It is reported that the dietary supplementations (for 8 weeks) with spinach, strawberry or blueberry extracts in a control diet were also effective in reversing age-related deficits in brain and behavioral function in aged rats. (Shukitt et al., 2008). 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 (Harikumar and Aggarwal, 2008). Grape polyphenol, resveratrol is very recent entry as an antiaging agent. It has been shown that the early target of the resveratrol is the sirtuin class of nicotinamide adenine dinucleotide (NAD)-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 (FOXO), which regulates the expression of genes that contribute both to longevity and resistance to various stresses and insulin-like growth factor binding protein 1 (IGFBP-1) (Barger et al., 2008). There are experimental evidences that resveratrol can extend lifespan 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).

3.4.5 Neuro-Protective Effects

Oxidative stress and damage to brain macromolecules is an important process in neurodegenerative diseases. Alzheimer's disease is one of the most common occurring neurodisorder affecting up to 18 million people worldwide. Because polyphenols are highly antioxidative 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 antioxidant activity is probably involved in the beneficial effect of the moderate consume of red wine against dementia in the elderly. Resveratrol inhibits nuclear factor κB signaling and thus gives protection against microglia-dependent β-amyloid toxicity in a model of Alzheimer's disease and this activity is related with the activation of the SIRT-1(Markus and Morris, 2008). 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 have invaluable potential agents in neuroprotection 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 neurological disorder characterized by degeneration of dopaminergic neurons in the *substantia nigra zona compacta*. Nutritional studies have linked the consumption of green tea to the reduced risk of developing Parkinson's disease. In animal models epigallocatechin gallate (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, due to molecular similarity or 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 antioxidant 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 antioxidant and detoxifying enzymes particularly in the brain, which is not sufficiently endowed of a swell-organized antioxidant 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).

3.4.6 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 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., 2003). Increased consumption of the soy isoflavone, 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 prevents 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. Theaflavins 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. HIV-1 entry into the target cell involves fusion of glycoprotein (GP) and envelope of the virus with the cell membrane of the host cells. Haptad repeat units present at N and C terminals of GP41 (membrane protein) on the viral envelope, fuse to form the fusion active GP41 core, which is a six-helical bundle. Theaflavins were found to block the formation of this six-helix bundle required for entry of the virus into the host. Theaflavin 3 3′ digallate, and theaflavin 3′ gallate were found to inhibit Severe Acute Respiratory Syndrome (SARS) corona virus. This antiviral activity was due to inhibition of the chymotrypsin like protease (3CL Pro) which is involved in the proteolytic processing during viral multiplication (Sharma and Rao, 2009).

Dietary sources of polyphenols exhibit anti-inflammatory, anti-carcinogenic (Kuroda and Hara, 1999), anti-antheronic (Dell Agli, Busciala and Bosisio, 2004) and cardio-protective effects (Visioli et al., 2000), linked with their antioxidant capacity. Protective effects on brain degenerative processes are also implicated by polyphenols (Conte et al., 2003). Anti-oxidants neutralize free radical reactive oxygen species that are generated endogenously through aerobic metabolism. These are potent genotoxins causing mutation, DNA strand breakage and oxidative damage to DNA, lipids and proteins both in vitro and in-vivo (Parker et al., 2007). The polyphenolic fractions of fruits and vegetables in particular, have been frequently linked with benefits to human health. The anti carcinogenic value of a diet high in fruit and vegetables may be due to the relatively high abundance of anti-oxidants in these foods which act to inhibit oxidative DNA damage through a variety of mechanisms including free radical scavenging and metal chelation (Duthie et al., 2000).

The levels of polyphenolic compounds present in fruits depend on cultivar, growth conditions (soil, fertilizer, temperature cultivation technique) storage and transport conditions and processing technology. Furthermore environmental stresses can elicit elevation of expression of vitamins and phenolics and associated increase in anti-oxidants potency for example in high altitudes, natural factors such as radiation, diurnal temperature difference, limited rainfall, soil, mineral content and wind induce metabolic stresses that lead to elevation of polyphenolic content of apricot). The anti-oxidant activity of food based poly-phenolics reflects the cumulative effects of chemicals and enzymatic process occurring either during processing and or storage. Chemical and enzymatic processes can lead to either loss of phenolic related anti-oxidant capacity or may generated chemical derivatives with inferior, unchanged or superior anti-oxidant activity (Nicoli et al., 1999).

3.5 Methods to assess anti-oxidants or anti radical activity

A wide range of methods has been elaborated or adapted to assess anti-oxidant or anti-radical activity of fresh fruits, including ferric reducing anti oxidants power (FRAP), Trolox equivalent anti-oxidant capacity (TEAC) 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity, and many others (Huang et al., 2008, Saribura et al., 2010). Total phenolic content (TPC) assay using the Folin-Ciocalteu's reagent can also be regarded as a single electron transfer anti-oxidant capacity assay (Huang and others 2005). Among hydrogen atom transfer reactions, oxygen radicals absorbance capacity (ORAC) and assays based on chemical luminescence detection are well known.

The existing anti-oxidants activity capacity essay methods in literature depending on the consumption of chromogenic radicals, i.e., ABTS and DPPH (Sanchez et al., 1998) matrices (Comogyi et al., 2007; Moon and Shibamoto 2009). However to determine the contribution of individual anti-oxidant in a mixture, time consumers and skillful work such as bioassay guided fractionation is required. So to avoid this problem, the high resolution screening system, the so called on line system, was developed by using HPLC combined with many different assays (Niederland et al., 2008). In these systems HPLC separates each constituent in the mixture and the HPLC flow from column reacts in the assay system. A colored, relatively stable radical such as DPPH and ABTS can be easily used in the assay system and anti-oxidants activity is collected as negative peak by a decrease in absorbance at visible wavelength to the conversion of radicals to their reduced non-color form (Ozen et al., 2006). Anti-oxidants being non-enzymatic defenses of the organism against reactive O, N species are essential for human health. Most anti-oxidants compound are introduced to the organism through diet. Therefore it is desirable to establish methods can directly measure the total anti-oxidant capacity of food plant extracts (Huang et al., 2002).

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