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# Dietary Polyphenols and Human Health

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**Abstract:** Polyphenols are substances of plant origin that occur in numerous fruits and vegetables, wine, tea, olive oil, chocolate and other cocoa products. They show antioxidant properties *in vitro* and many of their biological actions have been attributed to their intrinsic reducing capabilities. Research on the effects of dietary polyphenols on human health has developed considerably in the past 10 years. It strongly supports a role for polyphenols in the prevention of degenerative diseases, particularly cardiovascular diseases, osteoporosis, neurodegenerative, diabetes mellitus and cancers. The antioxidant properties of polyphenols have been widely studied, but it has become clear that the mechanisms of action of polyphenols go beyond the modulation of oxidative stress. Polyphenols are currently sold as nutritional supplements. Yet the scientific basis for the health claims for polyphenols is mostly weak. Results from *in vitro* studies are often directly translated into possible beneficial health effects in humans. However, in the body, polyphenols are quickly and easily converted into polyphenol metabolites. Presented review on Polyphenols and Health, offers an overview of the experimental, clinical and epidemiologic evidence of the effects of polyphenols on health.

**Key words:** Oxidative stress, antioxidants, neurodegenerative disorders, cardiovascular diseases, cancers, diabetes mellitus, apoptosis

## INTRODUCTION

### Source

Polyphenols are the most abundant antioxidants in the diet. Their main dietary sources are fruits (apples, cherries, pears, grapes, plums, strawberries, rasberries), Vegetables (broccoli, onion, cabbage), cereals and legumes. Plant-derived beverages such as fruit juices, tea, coffee and red wine and chocolate also contribute to the total polyphenol intake. Their nutritional effects have come to the attention in recent times. Before present century antioxidants were vitamins, carotenoids and minerals.

The phytochemicals in fruit and vegetables are different from those in the grains, which contains tocotrienols and tocopherols, while rice contains oryzanols. The phenolics like Ferulic acid and diferulate predominant in grains (Rapola *et al*., 1997; Lloyd *et al*., 2000). Ragi had the highest Total Phenol Content (TPC) among cereals/millets, while rice had the lowest. Among pulses black gram dal had the highest TPC, while green gram dal had the least. Ferric Reducing Antioxidant Property (FRAP) and reducing power were the highest in rajmah (Sreeramulu *et al*., 2009).

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**Classification**

Polyphenols contains more than one phenol unit per molecule. Polyphenols classified as:

- Hydrolyzable tannins (gallic acid, esters of glucose and other sugars)
- Phenylpropionoids (lignins, flavonoida)
- Condensed tannins (in leaves)

Polyphenols are also classified by the type and number of phenolic subcomponents present.

- Phenols (coumaric acid, kaempferol)
- Pyrolcatecol (catechin, quercetin, caffeic, ferulic acid and hydroxytyrosol)
- Pyrogallol (tannins, myricetin)
- Resorcenol (resveratrol)
- Phloroglucinol (flavanoids)
- Hydroquinone (arbutin)

The largest and best studied polyphenols are the flavanoids, which include the flavanols, flavones, flavanones, catechins, anthocyanidine, isoflavanoids. Condensed tannin comprising 50% of the dry weight of leaves. The phenolic unit can often be esterified and methylated. They can produce new compound through dimerization or polymerization. Gallic acid dimerized to form ellagic acid ellagitannins, or a gallocatechin and catechin a can combine to form the red compound theaflavin.

**Modes of Action**

Tannins were once believed to function as anti-herbivore, but now these are important controllers of decomposition, nitrogen cycling processes and regulators of carbon cycling. Polyphenols antioxidant's ability scavenges free radicals. These are reactive atoms that contribute to tissue damage in the body like LDL cholesterol when it gets oxidized; it can glue to arteries and cause coronary heart disease. Polyphenols also up-regulate certain metal chelation reactions. Thus various ROS (Reactive Oxygen Species) removed from cells to maintain healthy metabolic function. ROS have roles in redox signaling as linked to ion transport.

Due to continuous oxidative stress, DNA damage and change in signal transduction lead to cell mutation an expression of oncoprotein on to the cell surface. Tumour growth is supported by stimulating blood vessel development (angiogenesis). Blood flows within these new vessels is often disordered, causing hypoxia, followed by reperfusion, which causes the generations of ROS. Reactive radicals formed due to anticancerous therapies are partly responsible for the toxic effects (Klaunig and Kamenduis, 2004).

*In vitro* or animal experiments are often performed with much higher doses than those to which humans are exposed through the diet. Polyphenols clearly improve the status of different oxidative stress biomarkers (Williamso and Manach, 1993). Epidemiologic studies tend to confirm the protective effects of polyphenol consumption against cardiovascular diseases (Arts and Hollman, 2005). One of the major difficulties of elucidating the health effects of polyphenols is the large number of phenolic compounds found in food (Cheynier, 2005), yielding differing biological activities, as shown in several *in vitro* studies (Kuntz *et al*., 1999; Breinholt and Larsen *et al*., 1998). Major differences in bioavailability are now well established and the influence of structural factors is better understood (Manach *et al*., 2005).

Polyphenols are extensively conjugated in the body and nonconjugated metabolites most often account for a minor fraction of the circulating metabolites. Dietary polyphenols provided protection against age-related oxidative stress in human. Cells respond to polyphenols mainly through direct interactions with receptors or enzymes involved in signal transduction, which may result in modification of the redox status of the cell and may trigger a series of redox-dependent reactions (Halliwell *et al*., 2005; Moskaug *et al*., 2005; Forman *et al*., 2002).

**Distribution**

Plant polyphenols are products of the phenylpropanoid biosynthetic pathway and include ellagic acids, chalcones, flavonoids including the anthocyanins, coumarins and hydroxycinnamic and hydroxybenzoic acids. (+)-Catechin and (-)-epicatechin are widely distributed in foods. Catechin concentrations are especially high in broad beans, black grapes, apricots and strawberries. (-)-Epicatechin is found at high concentrations in apples, blackberries, broad beans, cherries, black grapes, pears, raspberries and chocolate. The gallates and the gallocatechins are found almost exclusively in tea, especially green tea. Procyanidins are oligomeric catechins, covalently linked together. They are present at high concentrations in cocoa, grapes/wine and apples and are also found in many fruits, such as blackberries, cherries, figs and plums. Flavonols (including quercetin) is found at high concentrations in onions, apples, tea, broccoli and red wine and as a component of Ginkgo biloba.

## USES OF POLYPHENOLS

The predominant effects of polyphenols are on the vascular system and substantial increases in plasma antioxidant activity, decreased platelet aggregation (both stimulated and unstimulated), decreased plasma concentrations of lipid peroxide and thiobarbituric acid-reactive substances, decreased LDL cholesterol concentrations, increased HDL cholesterol concentrations, decreased susceptibility of LDL to oxidation, endothelium-dependent blood vessel dilation and decreased blood pressure, beneficial effects on capillary fragility and permeability, increased plasma ascorbate concentrations, decreased P-selectin expression, increased concentrations of nitrosated/nitrosylated species, decreased serum thromboxane concentrations, increased diameters of microvessels, reduced serum thromboxane B2 concentrations, increased plasma homocysteine concentrations, increased plasma vitamin B6 concentrations, maintenance of endothelial function (compared with loss with a high-fat diet), increased platelet-derived nitric oxide production, decreased superoxide release, increased $\alpha$-tocopherol concentrations and decreased concentrations of circulating auto antibodies to oxidized LDL.

**Polyphenols as Antioxidant**

Molecule which can prevent the oxidation of other molecules is an antioxidant. During oxidation free radicals are produce, which can start chain reactions, which damage cells. Antioxidants break these reactions by removing free radical intermediates and inhibit other oxidation reactions by being oxidized themselves. Polyphenols have the potential to act chemically as antioxidants as their extensive conjugated p-electron systems allow ready donation of electrons or H atoms from the hydroxyl moieties to free radicals. Low levels of antioxidants cause oxidative stress and may damage or kill cells. Oxidative stress is thought to contribute to the development of a wide range of diseases like Parkinson's and Aizheimer's disease. Parkinsons's disease, the pathologies caused by rheumatoid arthritis, diabetes and neurodegeneration. During the oxidative stress in cardiovascular disease the

Low Density Lipoprotein (LDL) oxidation appears to trigger the process of artherogenesis, which results in artherosclerosis and finally cardiovascular disease. A low calorie diet may reduce oxidative stress (Larsen, 1993). There are some evidence to support the role of oxidative stress in aging in model organisms such as *Drosophila melanogaster* and *Caenorhabditis elegans* (Helfand and Rogina, 2003; Sohal *et al*., 2002) the evidence in mammals is less clear (Sohal, 2002; Rattan, 2006; Pez-Lluch *et al*., 2006).

Flavonols shown effects on antioxidant biomarkers, such as increased resistance of lymphocyte DNA to strand breakage, decreased urinary 8-hydroxy-2'-deoxyguanosine concentrations, increased plasma antioxidant capacity, decreased tissue inhibitor of matrix metalloproteinase-1 expression, altered renal function, improved prostatitis symptoms and improved oxidative resistance to LDL (Williamso and Manach, 1993).

**Polyphenols and Cardiovascular Disease**

Epidemiologic studies suggest that higher polyphenol intake from fruits and vegetables are associated with decreased risk for cardiovascular disease. Flavonoids improve endothelial function and inhibit platelet aggregation in humans. The vascular endothelium is a critical regulator of vascular homeostasis and endothelial dysfunction contributes to the pathogenesis and clinical expression of coronary artery disease. Platelet aggregation is a central mechanism in the pathogenesis of acute coronary syndromes, including myocardial infarction and unstable angina. For these reasons, the observed effects of flavonoids on endothelial and platelet function might explain, in part, the observed beneficial effects of flavonoids on cardiovascular disease risk (Joseph, 2005).

**Polyphenols and Cancer**

Catechins, a major group of flavonoids show potential to prevent cancer (Arts *et al*., 2001). There were statistically significant inverse associations between lung cancer risk and the flavonoids quercetin (onions and apples) and naringin (white grapefruit) intake (Marchand *et al*., 2000). Carcinogenesis induced by heavy metal exposure may be eliminated by daily consumption of antioxidant which can be obtained from polyphenols of fruits (Mishra *et al*., 2010).

Anticarcinogenic properties of green tea may be due to the antioxidant effect of epicatechins derivatives (ECDs). These are (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), (-)-epigallocatechin-3-gallate (EGCG) and (-)-epicatechin (EC). Each of these epicatechin derivatives was also effective in inhibiting photo-enhanced Lipid Peroxidation (LPO) generated by incubating epidermal microsomes in the presence of silicon phthalocyanine and 650 nm irradiation. However, at equimolar basis, EGCG, which is also the major constituent in GTP, showed maximum inhibitory effects compared to other ECDs. The antioxidant property of ECDs suggest that it may work as anticarcinogenic (Katiyar *et al*., 1994).

An aqueous solution of Green Tea Polyphenols (GTP) was found to inhibit Lipid Peroxidation (LP), scavenge hydroxyl and superoxide radicals *in vitro*. Concentration needed for 50% inhibition of superoxide, hydroxyl and lipid peroxidation radicals were 10, 52.5 and 136 $\mu g\ mL^{-1}$, respectively. Administration of green tea polyphenols (500 $mg\ kg^{-1}$b.wt.) to normal rats increased glucose tolerance significantly ($p<0.005$) at 60 min. GTP was also found to reduce serum glucose level in alloxan diabetic rats significantly at a dose level of 100 $mg\ kg^{-1}$ b.wt. Continued daily administration for 15 days of the extract produced 29 and 44% reduction in the elevated serum glucose level produced by alloxan administration. Elevated hepatic and renal enzymes produced by alloxan were found to be reduced ($p<0.001$)

by green tea polyphenols. The serum lipid peroxidation levels which was increased by alloxan and was reduced by significantly ($p<0.001$) by the administration of 100 mg $kg^{-1}$ b.wt. of green tea polyphenols. Decreased liver glycogen, after alloxan administration showed a significant ($p<0.001$) increase after green tea polyphenols treatment. GTP treated group showed increased antioxidant potential as seen from improvements in superoxide dismutase and glutathione levels. However catalase, lipid peroxidation and glutathione peroxidase levels were unchanged. These results indicate that alterations in the glucose utilizing system and oxidation status in rats increased by alloxan were partially reversed by the administration of the glutamate pyruvate transaminase (Sabu *et al*., 2002).

Red wine contains a complex mixture of bioactive compounds, out of them resveratrol appear to have health benefits. It helps in cancer prevention, protection of the heart and brain from damage, reducing age-related diseases such as inflammation, reversing diabetes and obesity. Resveratrol help to produce sirtuins (enzymes regulate the production of cellular components by the nucleus). Resveratrol exhibits therapeutic potential for cancer chemoprevention as well as cardioprotection. Apple polyphenol shows effect on human cancers, especially on lung cancer and prostrate cancer (Boyer and Liu, 2004).

**Polyphenols and Neurodegenerative**

Aging is the major risk factor for neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Oxidative stress is the main pathophysiology of these diseases. Oxidative stress can induce neuronal damages, modulate intracellular signaling, ultimately leading to neuronal death by apoptosis or necrosis. Thus antioxidants have been studied for their effectiveness in reducing these deleterious effects and neuronal death in many *in vitro* and *in vivo* studies. Increasing number of studies demonstrated the efficacy of polyphenolic antioxidants from fruits and vegetables to reduce or to block neuronal death occurring in the pathophysiology of these disorders. These studies revealed that other mechanisms than the antioxidant activities could be involved in the neuroprotective effect of these phenolic compounds (Ramassamy, 2006).

Neurodegenerative disorders/syndromes (viz., Alzheimer, Parkinson and Huntington disease), seem to result from increased oxidative stress and the inability of Base Excision Repair (BER) pathway to handle adequately the oxidative damage inflicted upon DNA (Rao, 2007).

Aging and the associated neurological disorders have a link to Base Excision Repair (BER) efficiency, thereby pointing out that repair of oxidative damage to DNA plays an important role in aging as well as age-associated neurodegenerative disorders. BER is compromised in brain cells with age and the two limiting factors appear to be pol $\beta$ and DNA ligase (Rao, 2009).

Increased oxidative stress in the brain due to chronic ethanol consumption is known to result in a number of neurodegenerative changes. Chronic ethanol caused significant decreases in synaptosomal Na, K-ATPase (20.5%) and dopamine uptake (22.8%) activities compared with pair-fed controls. Grape polyphenols (GP) supplementation was able to completely protect the decrease in synaptic protein function elicited by chronic ethanol consumption (Sun *et al*., 1999).

Antioxidant found in apples and some other fruits and vegetables protects brain cells against oxidative stress, a tissue-damaging process associated with Alzheimer's and other neuro degenerative disorders.

**Polyphenols and Diabetes Mellitus**

Cocoa polyphenols may offer diabetes benefits. Dietary supplementation with Cacoa Liquor Proanthocyanidins (CLPr) reduced blood glucose levels in obese diabetic mice and may offer human diabetics significant benefits (Tomura *et al*., 2007).

A polyphenol extract from a Corbières (France) red wine (P, 200 mg $kg^{-1}$), ethanol (E, 1 mL $kg^{-1}$), or a combination of both (PE) was administered daily by gavage for 6 weeks to healthy control or streptozotocin (60 mg $kg^{-1}$ i.v.)-induced diabetic rats (180-200 g). Treatment groups included C or D (untreated control or diabetic) and CP, CE, or CPE (treated control) or DP, DE, or DPE (treated diabetic). P treatment induced a reduction in body growth, food intake and glycemia in both CP and DP groups. In DP, hyperglycemia was reduced when measured 1 h after daily treatment but not at sacrifice (no treatment on that day). The hyperglycemic response to the Oral Glucose Tolerance Test (OGTT) and plasma insulin at sacrifice were impaired similarly in DP and D groups. In contrast, in DE or DPE, body growth was partially restored while hyperglycemia was reduced both during treatment and at sacrifice. In addition, hyperglycemia response to OGTT was reduced and plasma insulin was higher in DE or DPE than in D animals, indicating a long-term correction of diabetes in ethanol-treated animals. Morphometric studies showed that ethanol partially reversed the enlarging effect of diabetes on the mesenteric arterial system while the polyphenolic treatment enhanced it in the absence of ethanol. In summary, our study shows that (1) a polyphenol extract from red wine (used at a pharmacological dose) reduces glycemia and decreases food intake and body growth in diabetic and nondiabetic animals and (2) ethanol (nutritional dose) administered alone or in combination with polyphenols is able to correct the diabetic state. Some of the effects of polyphenols were masked by the effects of ethanol, notably in diabetic animals. Further studies will determine the effect of nutritional doses of polyphenols as well as their mechanism of action (Najim *et al*., 2004).

Anti-diabetic and antioxidant attributes of ethanolic extracts of *Butea monosperma* leaves were evaluated in alloxan induced diabetic adult male Swiss albino mice. Alloxan was reported to cause a significant reduction of insulin producing β-cells of islets of langerhans, thus inducing hyperglycemia (Sharama and Garg, 2009).

The increased blood glucose leveling diabetic mice (group II) as compared to normal ones (group I) might be due to glycogenolysis and/or gluconeogenesis (Guyton and Hall, 2000). Ethanolic extract of *Butea monosperma* ( BMEE) showed significant anti-diabetic and antioxidant potential in alloxan induced diabetic related oxidative stress and hence may find use for the management and/or control of diabetes (Sharama and Garg, 2009).

**Polyphenols as Nutritional Supplements**

Oxidative stress has been associated with osteoporosis. Most of commercially available nutritional supplement contains antioxidative polyphenols. The number of osteoblasts increases in human when cells were cultured in Ham's F-12 medium in the absence or presence of varying concentrations of Total Free Polyphenolic (TFP) in the extracts of nutritional supplement. They have beneficial effects on bone formation *in vitro* due to its antioxidant polyphenolic content (Rao *et al*., 2008).

The group of rats receiving herbal supplement after jaundice induction have shown lower extent of Lipid Peroxidation (LPO), compared to the rats receiving phototherapy only. The 4-hydroxynonemal (HNE)-protein adduct formation in the liver is also found to be lower in the herbal extract-treated rats compared to the untreated rats. The herbal extract probably scavenges the Reactive Oxygen Species (ROS) generated at the high bilirubin level, reduces its deleterious effect and induces the antioxidant activity of the bilirubin itself (Nag *et al*., 2009).

Extract from spent/waste part of *vetiveria zinzanoides* L. may find use as dietary/supplementary antioxidant in neutraceuticals and cosmoceuticals for protection against complications arising from the oxidative stress (Luqman *et al*., 2009).

**Polyphenols and Apoptosis**

Green tea polyphenols attenuated the NO-induced apoptotic cell death, assessed by cell viability, Hoechst staining and terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labeling staining. The protective mechanism was via elevated expression of the antiapoptotic bcl-2 gene and suppressed expression of the proapoptotic bax gene, thereby arresting NO-induced apoptotic cell death. Furthermore, GTP appeared to be a potent inhibitor of acetylcholinesterase, exhibiting an IC50 of 248 $\mu g\ mL^{-1}$. This report is showing the inhibitory effect of GTP on acetylcholinesterase activity. This potential can be used to cure neurodegenerative disease (Chung *et al*., 2005).

**Other Uses**

Apple polyphenol have been shown more powerful antioxidants properties then vitamin C and are also showing promise in improving skin disorders, treating baldness in males and preventing allergies. Isoflavones (genistein and daidzein) effects on bone biomarkers, such as significant increases in bone mineral density and bone mineral content and changes in bone biomarkers, such as reduced excretion of pyridinium cross-links and increased serum concentrations of bone-specific alkaline phosphatase and osteocalcin. Other effects include changes in LDL and HDL cholesterol concentrations, increases in LDL oxidation lag time and changes in menopausal symptoms and hot flashes.

## CONCLUSION

Oxidative stress, whether over-excitation, excessive release of glutamate or ATP caused by stroke, ischemia or inflammation, exposure to ionizing radiation, heavy-metal ions or oxidized lipoproteins may initiate various signaling cascades leading to apoptotic cell death and neurodegenerative disorders. Several polyphenols and antioxidant drugs are effective in protecting the cells from ROS attack. Further development of these antioxidant molecules may be of value in preventing the development of neurodegenerative, cardiovascular diseases, diabetes mellitus and cancers. Dietary polyphenols are the excellent preventive measure for many diseases and disorders thus are essential for human.

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