

Polyphenols: Nature's Gift as Dietary Phytoconstituents Against Different Human Ailments

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Abstract

Recently, researches and scientists are showing a lot of interests in bioactive compounds of plants and its products as these constituents are of high valued. Polyphenols are phytochemical constituents which are the integral components in plants and their products that are associated with defensive mechanism against infections and various oxidative stress by free radicals. Green tea, fruits, vegetables, cereals and red wines are rich sources of polyphenolic constituents which attributes prevention from infections and diseases because of its antioxidant properties, anti-diabetic properties, and radical scavenging properties. Oxidative stress which is the primary reason for different ailments in humans is due to the free radicals that are present even during the normal health condition. Polyphenolic acids like cinnamic acid, rosmarinic acid, stilbenes like resveratrol, flavonoids like catechin, taxifolin, quercetin, and lignans like sesamin, pinoresinol, podophyllotoxin etc. are found to be effective against wide range of human diseases like oxidative stress, cardiovascular disorder, neurodegenerative diseases, aging, and cancer. These phytoconstituents prevent the diseases and provide relieving sensation via different mechanisms. Here, the study shows the importance of polyphenols with respect to the relevance of human health. As there are the promising applications of various bioactive constituents in a wide range of disease, further research should be encouraged on the mechanism of action and bioavailability of polyphenols.

Keywords Polyphenols; Antioxidants; Bioavailability; Cardiovascular diseases; Diabetes; Aging; Cancer

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Introduction

Plants produce different secondary metabolites among which polyphenols are of great importance, which is engaged in protection from various pathogens and radiation [1]. Polyphenols occur abundantly in fruits and vegetables that we consume in daily lives [1-3]. Food consists of polyphenols which attribute to the astringency, taste, coloration, and oxidative stability [3-4]. Past research and study strongly provide evidence that the constant dietary intake of food with exuberant polyphenols provide defence against various diseases like diabetes [5], cancer [6], cardiovascular diseases [7] and neurodegenerative diseases [8] (**Figure 1**) As the food with phenols and its derivatives are propitious to health, polyphenols and its derivatives demands are augmenting.

Classification of Polyphenols

Around 10,000 polyphenolic compounds have been discovered and identified [9]. Almost all

Polyphenols originate from a basic precursor, phenylalanine or shikimic acid. Phenylalanine is a substitute for methyl group of alanine whereas Shikimic acid is a cyclohexane, an anionic form of shikimate [9-10]. Normally, these precursors are associated with sugar residues in association with hydroxyl groups, carboxylic acids, organic acids, lipids, amines, etc. On the basis of phenol ring possessed by phenol and on the basis of structural components that they incorporate, phenols can be classified into different groups [11]. Most important classification of polyphenols includes phenolic acids, stilbenes, flavonoids, and lignans [9-11]. Illustration of different classes of polyphenols is provided by **Table 1**.

Phenolic Acids

These are aromatic acid compounds which comprises a phenolic ring and an organic carboxylic acid framework. These are found



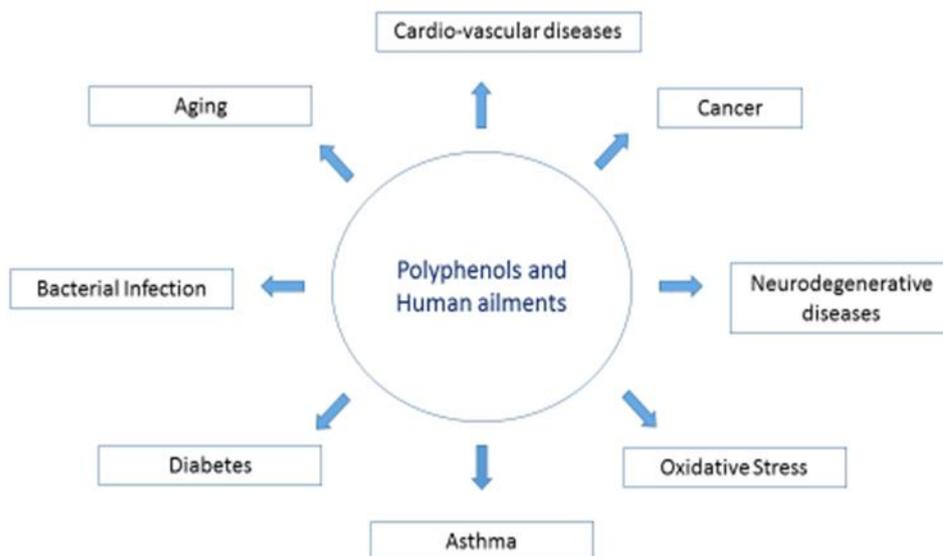


Figure 1: Polyphenols found abundantly as plant secondary metabolites occurring naturally in vegetables, fruits, cereals, green tea and red wines. Research and studies have shown that plant extracts are rich in polyphenolic constituents which are potent radical scavengers and impart great antioxidant activities providing significant protection against wide range of diseases like cardiovascular diseases, cancer, neurodegenerative diseases, aging, and diabetes.

Table 1. Types of polyphenols: Sources and functions

Polyphenols	Food Sources	Examples	Functions	References
Phenolic acids	Straberries, coffee, nut, vinegar, turmeric, rosemary, cinnamon	Cinnamic acid, ellagic acid, rosmarinic acid	Antioxidant, Radical scavengers and anti-carcinogenic activities	12-14
Stilbenes	Grapes, red wine	Resveratrol	Reduce oxidative stress, anti-aging, antioxidants.	15-16
Flavonoids	Green tea, onion, berries, citrus fruits. Apple	Catechin and epicatechin, taxifolin, quercetin	Antimicrobial, antioxidant and antidiabetic	17-18
Lignans	Wide variety of plant species	Podophyllotoxin and its derivatives	anticancer therapy	19-20

copiously in fruits and vegetables and are further divided into two naturally occurring broad classes of hydroxybenzoic acids (**Figure 2**) and hydroxycinnamic acids (**Figure 3**) that are synthesized from the non-phenolic component of benzoic and cinnamic acid respectively [21]. The study has shown that the content of hydroxybenzoic acid in the case of an edible plant is usually low, except in the case of red fruits and onions. Clearly, hydroxycinnamic acids are found more commonly than hydroxybenzoic acids [22]. Phenolic acids are found in greater amount in dried fruits, beans, mushrooms, chicory, coffee etc. (21-22).

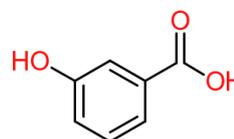


Figure 2: 3-hydroxybenzoic acid

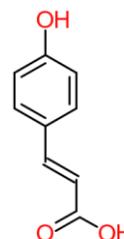


Figure 3: hydroxycinnamic acid

Stilbenes

Stilbenes consists of two phenyl components united via two carbon Methylene Bridge.

Stilbene may be either E-stilbene (trans-isomer) (**Figure 4**) or Z-Stilbene (cis-isomer) (**Figure 5**) (23). E-stilbene consists a central ethane double bond replaced with phenyl groups on each carbon atoms of double bond whereas in Z-stilbene it consists of cis ethane double bond substituted by a phenyl group on both carbon atoms of the double bond. Human diet contains a low amount of stilbene [24]. The most widely researched stilbene is resveratrol, which occurs naturally. Red wines and grapes comprise a higher number of stilbenes.

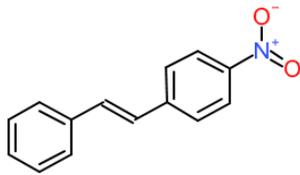


Figure 4: (E)-4-nitrostilbene

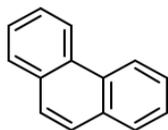


Figure 5: Z- Stilbene

Flavonoids

Flavonoids (**Figure 6**) are bioactive polyphenols which have low molecular weight with the 15-carbon skeleton, which comprises two phenyl rings and a heterocyclic ring. Flavonoids are the most indispensable group which is studied widely and they can again be classified into thirteen different subclasses [25].

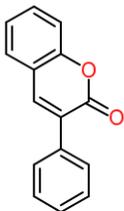


Figure 6: Flavonoids (benzyl pyrone)

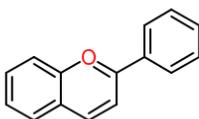


Figure 7: Anthocyanin

Over 4,000 flavonoids have been discovered and studied, most of which gives pigmentation to flour, fruits, and leaves. Flavonoids which

are of eminent importance include flavonols, flavanones, isoflavones, flavones, and anthocyanins (**Figure 7**) [25-26].

Lignans

Lignans contain a structure which is derived from dimerization of two cinnamic acid residues (**Figure 8**). Lignans are derived from 2 phenyl propane moiety and sound plant source is vegetables, cereals, lentils and linseed [27]. Among the listed sources of lignans, linseed is the richest one. Major constituents of lignan include Seco iso lariciresinol and minor being matai retinol [27-28].

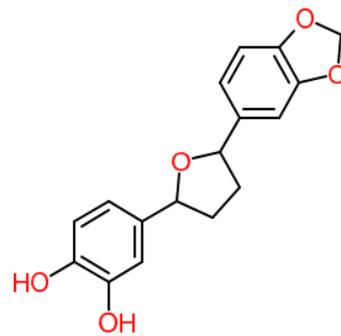


Figure 8: Lignans

Recent Findings

Polyphenol consumption

Regarding the dietary consumption polyphenols, little research has been done, though it is of immense importance. On a study carried out in the USA, flavonoid consumption was found out to be approximately 1gm/d [29]. Among various groups of polyphenols, the flavonoid is studied widely. Daily intake of flavonoids has been estimated to be approximately 20 mg/d in European countries [30]. In Asian countries, there is significant consumption of soya which amounts to approximately 30 mg/d of isoflavones [30]. Dietary intake of polyphenols increases when vegetables and fruits like apple, pears, grapes etc. are consumed in the significant amount [29-30]. The worldwide consumption of tea and coffee aids in consumption of hydroxycinnamic acids. People who drink several cups of tea or coffee might intake approximately 700 mg hydroxycinnamic acids /d, whereas people who don't drink tea or coffee do not intake even

25 mg/d [31]. There is a variation on polyphenol intake and this is due to the individual preferences on different food items. In conclusion, polyphenol intake normally reaches 1g/d if people are subjected to adequate fruits and vegetables on daily basis [29-31].

Bioavailability of Polyphenols

The term “Bioavailability” is used to describe the perception of the speed and degree to which a metabolite approaches its spot action. In simple words, it is that portion of an ingested component which barges into the systemic circulation and distinct areas where it can employ its action [32-34]. The ultimate aim of bioavailability is to find out better-ingested components, active metabolites, and polyphenols that lead to the formation of the active metabolite.

Table 2. Important factors affecting bioavailability of polyphenols

Factors	Examples	References
Intestinal factors	Enzyme activity, intestine and colon microflora	33, 35
Systemic factors	Age, physiological condition, and diseases	33, 36
Food factors	Fat, fiber and food matrix	33, 37
Processing factors	Heat, homogenization and cooling methods	33
Other components	Bond with polyphenols or proteins	33, 38

In order to demonstrate the biological properties polyphenols essentially rely on bioavailability. The structural framework plays an important role in the rate at which these polyphenols are ingested in intestines [39]. Although some polyphenols are absorbed in small intestine, a great number of polyphenols that we intake cannot be readily absorbed in its original nature. In order to be absorbed, polyphenols have to be modified via intestinal enzyme and microflora present in it [40]. Polyphenols are hydrolysed in intestinal cells

and also the modification continues at liver via sulfation, glucuronidation, and methylation [41]. It is not the quantity of polyphenol that we consume determine the speed of absorption, but the chemical structure. It is a detoxification process that limits their toxic effects [39-41]. In addition to that, it facilitates biliary and urinary excretion by augmenting their hydrophilicity. Some of factors that affect bioavailability of polyphenols are listed on **Table 2**.

Polyphenol as the natural antioxidants

A molecule which has the capacity to inhibit the oxidation of other molecules is called antioxidants. During the oxidation process, there is the transference of electrons or protons from reference substance [42]. Oxidation process elicits free radicals which have the capability to start the deleterious reaction in the cell which ultimately deteriorates cell and in worse scenarios may lead to cell death [42]. Antioxidants, on the other hand, has the ability to terminate this deleterious reaction by scavenging the free radicals and by inhibiting the oxidation process [43]. Polyphenols are robust antioxidants and are depicted as free-radical scavengers [44]. This property is due to their hydrogen donating ability. Polyphenols provide H⁺ atoms readily. This free radical scavenging property is mainly due to its immense reactivity of hydroxyl components [45].

Polyphenols and cardiovascular Diseases

Cardiovascular diseases are mostly seen as a causative factor for mortality in developed countries [46]. Different factors are responsible for the coronary heart diseases out of which environmental and hereditary are the most prominent ones [47]. Besides genetic factors, lifestyle and the way of living and food consumption play important role in case of cardiovascular diseases [48]. Lack of physical activities, unhealthy food habits, the intoxication of the body with cigarettes & alcohol and stress full life are the main

contributing factors for the prevalence of cardiovascular diseases [49].

Different research and studies have shown that diet rich in polyphenols and flavonoids like beans, fruits and vegetables have curative and inhibitory effects against cardiovascular diseases [50-52]. It was observed from the study that, there was 11% reduction from the adverse effect of cardiovascular diseases when three cups of black tea are taken daily [53-54].

Cardiovascular diseases are prevented by the polyphenols because it has the ability to ameliorate the activity of an enzyme and increase the bioavailability of nitric oxide for endothelium [47-49]. Consumption of polyphenol-rich food products has a relaxing effect on the endothelium. Furthermore, food products rich in polyphenols like, flavonol has the effect of reducing hypertension and also lowers the blood pressure with improved function of endothelial tissues which prevents aggregation of platelet and lowers inflammation [55-56]. As black tea and cocoa contain high polyphenolic content, high drinking of these products lowers the risk of high blood pressure. [57-58]

Polyphenols and cancer

Cancer is a multi-step process. This includes initiation, development, and metastasis. Tumour may or may not cause deteriorating effects to the cell. Once the initiation starts, it inevitably progresses to malignancy imparting negative effects. Afterward, these cancerous cells transfer from one part to another by the process known as metastasis [59].

Polyphenols have the protective function and elicit the decrease in initial stage tumors. Different studies have shown that polyphenolic constituents like phenolic acids [60], stilbenes [61], flavonoids [62], phenol [63] and lignans [64] have proved to be effective against different human cancer cell lines. Polyphenol is to know for their inhibiting properties to cancerous cells via different mechanisms, which can be estrogen activity, antiproliferative activity, programmed cell death (apoptosis), Limiting oxygen to the cancerous cell, production and synthesis of detoxifying

enzymes, alteration in cell signaling and regulating immunity-inducing factors in the host [65-66].

Cancerous cells are the results of carcinogens which are activated by the assertion of cytochrome P450, but the polyphenols have the tendency to affect this activity and have been identified as inhibiting factor which restricts this promotion of P450 expression [67-68]. Polyphenols induce phase II proteins which detoxify the toxicity and engender enhanced immunity against harmful xenobiotics [66]. A study in green tea has revealed that its components like catechins, theaflavins, and cherubins have promising potential against cancer [69]. They have found to restrict the formation of cancerous cells by the programmed cell death of prostate cancer cells. Similarly, Quercetin and resveratrol have found to inhibit all stages of cancer development and have found to be advantageous against skin, lung, colon, and breast cancer [70].

Polyphenols and diabetes

Diabetes is a condition which leads to increase in blood sugar level in the blood. According to NLH, two main types of diabetes [type 1 and type 2) are common, type 2 being common [<https://medlineplus.gov/diabetes.html>].

Polyphenolic compounds work against diabetes by inhibiting the intestinal glycosidases and glucose transporter [72]. Different types of polyphenols like phenolic acids, stilbenes, flavonoids, phenol, and lignans are found to inhibit the S-Glut-1 transfer of glucose in the small intestine [72-73]. Resveratrol and saponins also have been found to detain the transport of glucose in the alimentary canal. Different studies have shown that quercetin, resveratrol, catechin, epicatechin, and epigallocatechin have anti-diabetic properties [74]. Stilbene too has potent antidiabetic property and controls diabetes by modulating SIRT1 which is responsible for homeostasis of insulin and glucose [75]. Report on LLC-PK1 cells shows that anthocyanins and grape juice have inhibiting effect towards

glucose mediated oxidative stress and cytotoxicity [76].

Polyphenols and aging

Different theories have been proposed regarding aging among which oxidative stress due to free radicals is one of the most approved ones [77]. Oxidative stress and detrimental effect due to it is present even under good health condition, but the damage rate elevates at the age increases due to weak repair mechanism at old age [78]. Aging is the consequence of the wide range of deleterious alteration in the cells as the age progresses ultimately leading to weakness and death [79]. Antioxidant and anti-inflammatory compounds have properties of reducing oxidative stress by scavenging the free radicals which work as effective anti-aging compounds [80]. Studies show that anthocyanins and grape polyphenol resveratrol show high scavenging potential with high antioxidant as well as anti-inflammatory activities [84]. They are known to restricts the peroxidation of lipids and also inhibit cyclo-oxygenase which is inflammatory mediators [80-83].

Dietary intake rich in flavonoids and polyphenolic compounds like fruits and vegetables shows high antioxidant activity. Berries, beans, spinach, apple and green tea have been reported with high antioxidant contents and found advantageous against age-related senescence and age-related problems [85-86]. Adequate consumption of polyphenols ameliorate the negative effects of aging and also have been found to delay the onset of aging [87].

Polyphenols and Neurodegenerative Diseases

Neurodegenerative diseases are the consequences of oxidative stress and free radicals which damage brain cells [88]. Medicine plus list 7 diseases under degenerative nerve diseases which include: Friedreich's ataxia, Alzheimer's disease, Parkinson's disease, lateral sclerosis, Huntington's disease, Amyotrophic, Lewy body disease and Spinal muscular atrophy.

Neurodegenerative diseases can be fatal even leading to the demise of patients.

Polyphenolic compounds are seen to have positive effects on nerve degenerative diseases as it has the power to scavenge the free radicals which impart detrimental effects in the body. Resveratrol, the integral component in grapes and wine, have been reported to scavenge free peroxide, hydroxide and other free radicals [90]. People who drink 2-3 glasses of red wine daily have been shown to 80% decrease in the evidence in Alzheimer's disease [91]. Drinking green and polyphenolic-rich diet act potent agent for neuroprotection via cell signaling, programmed cell death [apoptosis] proliferation and differentiation [92]. Green tea has been found effective against Parkinson's diseases by inhibiting MPTP (N-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine), which is the integral factor for Parkinson's diseases [91-93].

Conclusion

This review tries to outline the current understanding of polyphenols and its biological beneficial effects in human health. Dietary intake of polyphenolic compounds daily imparts important protection against wide range of detrimental diseases like cardiovascular disorders, diabetes, cancer, aging and nerve-degenerative diseases. This positive advantageous aspect of polyphenols on human health depends on their intake and their bioavailability. It is well documented through studies and researches all around the world that polyphenols have the wide range of applications in human health but still the mechanism of action of various polyphenolic constituents are yet to be understood. This positive advantageous aspect of polyphenols on human health depends on their intake and their bioavailability. The role of polyphenols in human health is a promising area of the research study. This review outlines the promising wide range application of polyphenolic compounds and prominent hope for chronic detrimental human diseases.

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