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Article

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Phenolic Substances in Foods and Anticarcinogenic Properties: A Public Health Perspective

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Abstract

The interest in polyphenols from vegetable sources has been progressively increased because of the demonstrated correlation between their abundance in certain foods or food preparations of traditional importance and heritage, and the answer of anti-inflammatory strategies in hospitalized patients in the presence of polypehnol-rich foods (as a complementary therapy). Consequently, research involving the accessory role of polyphenols as anti-tumoral aids have been carried out with the aim of finding new additional strategies. The purpose of this paper to evaluate the role of phenolic compounds in foods with reference to health effects for human beings. The importance of these molecules has been evaluated by the health and safety perspectives in terms of: fight to cardiovascular diseases; prevention of chronic-degenerative disorders; general antioxidant properties; and anticarcinogenic features. Moreover, the role of polyphenols-rich foods as anticancer agents has been discussed with relation to two distinct "action plans" on the public hygiene level: the promotion of human health on the one side (for non-hospitalized and normal subjects), and reliable contrasting strategies in cancer patients.

Polyphenols consist of a family of about 5000 natural organic molecules, characterized by the presence of multiple associated phenolic groups in more or less complex structures generally of high molecular weight. Their absorption and metabolism varies according to the phenolic fat.

In general, phenols are ubiquitous compounds in vegetables and fruits, including naturally transformed products from these sources. For this reason, many beverages are very often correlated with antioxidant properties such as fruit juices, teas, wines, etc. (1–5). These properties have justified and currently

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justify the importance of polyphenol-rich foods and beverages when speaking of food hygiene and medical approaches. Their importance has been widely recognized with reference to commercial and labeled claims indirectly linked with polyphenols as additives or ingredients of complex food mixtures, nutritional declarations, fortified food preparations, limitations of regulatory nature, various health and hygiene topics and worries (6–14), and methods for analytical determinations (15–20).

In the context of chronic degenerative diseases, it has been reported that foods rich in polyphenols may have beneficial effects against diabetes, cancer, and cardiovascular dysfunctions. Most likely, these properties are dependent on the antioxidant behavior of phenolics in general: consequently, peroxidation of fat matter is influenced notably.

In addition, phenolic compounds are reported to exhibit certain *in vitro* biological effects in the last ten years. Detail examples may include the absorption of cholesterol or the influence of enzymatic actions by acting on signal transduction. However, these effects should be evident *in vivo* if active molecules are able to reach the target tissues, and this aspect of the problem (abundance in foods vs. bioavailability) should be taken into account.

Main Factors Influencing Polyphenol Bioavailability

Taking up the concept of the bioavailability of polyphenols, it should be emphasized that it is difficult to quantify it in absolute terms, since there are several factors that could affect its effect. These factors can directly or indirectly influence bioavailability. The *in vivo* approach mostly used is named "single-dose design." It involves taking a portion of foods containing the tested polyphenol. In this way, the increase in blood concentration is transient and mainly reflects the body's ability to take polyphenol from the food matrix. As a result, the observed increase may have only a minor implication for tissue absorption and relative bioactivity. On the contrary, in conditions of regular intake, even small amounts of polyphenols can be "repeatedly" absorbed and can significantly increase concentrations both at the cellular and plasma levels.

Polyphenols and Cardiovascular Diseases

It is believed that polyphenols have a preventive effect on the development of cardiovascular disease (CVD), a concept that is supported by the so-called "French paradox." In fact, in this population it was noted that, despite the consumption of large quantities of milk fat (which we know is closely related to a greater number of CVD deaths), the mortality rate for CVD in France is lower, presumably because of the remarkable wine consumption if compared to other European countries.

Taking into consideration the French paradox, the polyphenols contained in wine (*trans*-resveratrol) and the epidemiological studies on the development of the disease conducted in different countries, it was found that the mortality rates for CVD were inversely proportional to the intake of polyphenols with the diet (21). Although the French paradox is generally considered to be related to the consumption of red wine, typical of France, a recent study has shown that the French paradox can also be applied to Mediterranean regions (22). The etiopathogenesis of cardiovascular and cerebrovascular diseases is often attributable to vascular dysfunction of endothelial cells (EC).

In the studies carried out on polyphenols, they have been recognized as useful for regulating the production of nitric oxide and endothelin-1 (ET-1). Furthermore, epi-gallocatechin-3-gallate inhibited the expression of adhesion molecules by a signaling pathway similar to that of high-density lipoproteins and involves the induction of calmodulin-dependent Ca2þ/kinase II, hepatic kinase B, and the expression of phosphatidylinositol 3-kinase.

The effects of polyphenols on vascular dysfunction of endothelial cells include antioxidant activity and increased expression of several protective proteins, including endothelial nitric oxide synthase and paraoxonase 1 (PON 1). However, the observed effects of *in vitro* food polyphenols they do not always translate into a living environment. Many questions therefore arise concerning their physiological mode of action. It has been shown in epidemiological studies that polyphenols have inhibited vascular cell lesions, including defects in vascular endothelial cell (EC) functions, and have been found to have a preventive effect on CVD (23).

In *in vitro* studies, protective actions of polyphenols against EC and vascular smooth muscle cells (SMC) have been also demonstrated. These reports indicated that polyphenols help maintain normal EC functions and contribute to an inhibition of CVD. In fact, polyphenols have an antioxidant effect on the vessels: they induce the formation of nitric oxide (NO). In addition, the role of enzymes such as nitric oxide synthase (eNOS) and prostacyclin (PGI2) strongly depend on the bioavailability of polyphenols (24, 25).

An important example is represented by polyphenols commonly found in red wines: their presence is correlated with the increase of NO and the concomitant release of alkaline metal calcium (26). PGI2 and ET-1 levels are also influenced when speaking of bioavailable phenolics such as quercetin (flavonol) (27).

Polyphenols, Antioxidant Action, and Cancer Prevention

Green tea flavanols (catechins) account for 30% of the dry weight of new tea leaves (28). The main components of the green tea catechin are epi-gallocatechin-3-gallate (EGCG, Figure 1) and epicatechin (29). Many studies have affirmed the effect of green tea in cancer prevention and it is believed that these compounds have anti-inflammatory, antibacterial, antioxidant, and anti-angiogenic activity (30, 31).

Many of these effects are attributable to EGCG (32). In EC vascular cells derived from human aorta, the addition of EGCG at low concentrations (2.5 mM) inhibited TNF-a induced VCAM-1

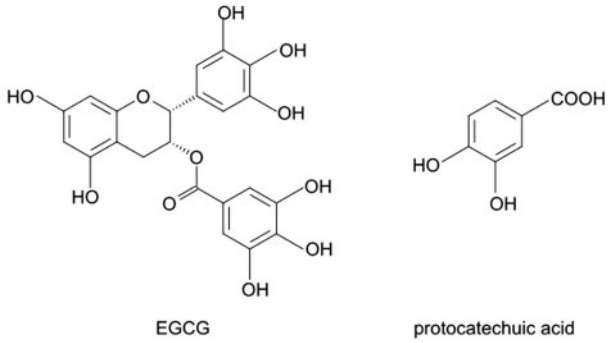

Figure 1. The chemical structure of two phenolic compounds with possible anti-inflammatory, antibacterial, antioxidant, and anti-tumoral activity: epi-gallocatechin-3-gallate (EGCG) and protocatechuic acid. BKchem version 0.13.0, 2009 (http://bkchem.zirael.org/index.html) has been used for drawing this structure.

expression, whereas the expression of heme oxygenase-1 was significantly increased (33). Furthermore, by examining the effects of several inhibitors, the protective action of EGCG against TNF-α-induced VCAM-1 expression was shown to be associated with MAPK-Nrf-2 and p38-dependent pathways as well as increased heme expression oxygenase-1.

Furthermore, EGCG promotes NO-dependent vasodilation in EC through a mechanism involving the SRC family kinase (but not Src) which led to the activation of PI3K, AKT and eNOS with ROS production (34). These results may explain the beneficial effects of green tea consumption on EC vascular function. 7-ketocholesterol (7KC) induces monocytic adhesion to ECs, which in turn induces arteriosclerosis. Adhesion of monocytic cells induced by 7KC was accompanied by increased expression of ICAM-1 and MCP-1.

EGCG has a protective effect against arteriosclerosis, which may be due to its ability to block the adhesion of 7KC-dependent monocytic cells to ECs, and to induce the expression of eNOS as well as several genes involved in the CaMKKII pathway (35). The action of EGCG in this setting has been associated with changes in the expression of genes such as CaMKKII, LKD1, and PI3K, which in turn could influence ROS production (36). CaMKKII, LKD1, and PI3K participate in signaling pathways that are important for the effects of HDL in ECs (36). Furthermore, ROS production is a significant feature of EGCG action.

Similarly, one study indicates that the addition of interleukin (IL) and b-carotene carotenoid, or both, to human EC cultures also co-induces the expression of CaMKKII, PI3K, PZK1, LKB1, eNOS, and PON1, reducing the expression levels of ICAM-1 and MCP-1. Furthermore, b-carotene induced phosphorylation of 50 kinase proteins activated with adenosine monophosphate (AMP) -activated (p-AMPK), eNOS (p-eNOS), and PON1.

Functional Components: The Antioxidant Action and Anti-tumoral Potential

At present, the role of a healthy diet is very important in the prevention of non-communicable diseases, and the border between food and medicine is becoming very thin (37). Actually, functional components appear different enough.

Scientific research has shown a relationship between various functional components present in food and the improvement of health and well-being (38). As a result, functional components have roles promoting health at various stages of disease control. These functions are associated with multiple stages. Therefore, they can be effectively applied in the treatment and prevention of diseases (39).

Functional food components include non-nutritive and biologically active phytochemicals from vegetable sources (40). Functional components were initially thought to occur predominantly only in plant foods, including whole grains, fruits, and vegetables. However, probiotics, conjugated linolenic acid, bioactive peptides, and different polyunsaturated (ω-3,-6, and -9) fatty acids are also found in animal products such as milk, fermented milk-based products, and cold-water fish. With exclusive relation to polyphenols, the most known of these molecules are anthocyanins, catechins, flavonoids, isoflavones, lignans, tannins (proanthocyanidins), stanols, and sterols (41), generally obtained from vegetables and fruits. Several functional components are obtained also from salmon and other fish oils, in cheeses, and in some meat products. However, phenolics are often correlated with vegetable sources.

Potential advantages of these bioactive components include the neutralization of free radicals able to damage cells, with the reduction of muscle degeneration risks and different (prostate, breast, and colon) cancer. They are also very useful in immune modulation, in apoptosis of tumor cells, with reference to the stimulation of human brain development. Functional foods have anti-coagulant effects, also lowering cholesterol levels in blood.

Role of Polyphenols as Bioactive Agents in Functional Foods on Critical Enzymes Related to Degenerative Diseases

Chronic-degenerative diseases such as cancer, platelet aggregation, thrombosis, sexual dysfunction, arthritis, diabetes, obesity, stroke and respiratory, cardiovascular, and neurodegenerative diseases are among the main causes of morbidity and mortality worldwide (42). Degenerative diseases have a strong impact on health, quality of life and life expectancy (43). These diseases are rapidly spreading around the world and have contributed to about 60% of the 56.5 million total deaths recorded in the world and about 46% of the global disease burden (42). CVD and cancer are the first two main causes of death in many countries (44). Epidemiological and experimental studies have shown that high consumption of fruit, vegetables, spices, drinks, legumes, and whole grains in a diet that is often at high risk, together with other food products can be strongly linked to the reduction of the risk of chronic diseases such as CVD, cancer, diabetes, Alzheimer's disease, sexual dysfunction, cataracts, and age-related functional decline (45).

Neurodegenerative diseases are characterized by a loss of neuron integrity from the brain and spinal cord for a period of time and could lead to dementia (46). The aging process originating from the excessive production of reactive oxygen species (ROS) has been attributed to the global increase in neurodegeneration (47). Theories of aging mechanisms have suggested that cumulative oxidative stress could cause mitochondrial dysfunctions and oxidative damage leading to neurodegenerative diseases, characterized by memory disorders and cognitive dysfunctions (48). In this ambit attention has recently been shifted from scientists and researchers in the food industry to tropical plant foods with phytochemicals rich in antioxidants and healthy as potential therapeutic agents (49). Both experimental and epidemiological evidence have indicated that consumption of vegetables, fruit, tea, spices, and herbs is associated with low risk of various neurodegenerative diseases (50, 51). As a single example, the investigation on the possible effect of protocatechuic acid (Figure 1) revealed that the activity of the antioxidant enzyme Na^+/K^+-ATPase, cholinergic, and antioxidant is altered by protocatechuic acid in rats (52, 53). It has also been reported that alkaloid extracts from shea butter and bread were able to inhibit monoamine oxidase, cholinesterase, and lipid peroxidation in an in vitro model (54).

Conclusions

The interest in dietary polyphenols has been stimulated mainly by epidemiological studies that indicate an inverse association between the intake of foods rich in these compounds and the incidence of diseases, such as cardiovascular diseases, diabetes mellitus and cancer. Epidemiological evidence related to the benefit of consuming a diet rich in foods containing polyphenols appear evident.

Nutrition can help prevent chronic pathophysiological conditions including diabetes, cancer, atherosclerosis, and cardiovascular and neurodegenerative diseases. The Mediterranean

diet has been associated with a reduced incidence of neurodegenerative diseases and improved cognitive performance. This has attracted the attention of researchers and there have been a number of studies that seek to identify which components and micro-constituents of this diet, including phenolic compounds, are responsible for these beneficial health effects. One of the active compounds present in olive oil that could be, in part, the cause of the neuroprotective effects attributed to the Mediterranean Diet. Some other minor components of olive oil (triterpenes and oleocanthals) have also been briefly considered. It is clear that some caution is required before attributing biological activities to a compound. Resveratrol has not shown activity in humans, in spite of the evidence of biological effects. This fact shows that some interesting results that occur in *in vitro* studies and in animals, cannot be always be considered when speaking of human health.

Phenolic compounds of vegetable origin seem to be safe enough and interesting principles in the context of nutraceuticals with higher doses than those compatible with the Mediterranean Diet. In-depth analysis of pharmacokinetic properties and safety profile may propose phenolics as good potential therapeutic candidate for the prevention of neurodegenerative diseases and cancers. However, further applied research in humans is needed to verify that discoveries in research laboratories can be translated into practical clinical recommendations. It is obvious that other components and lifestyle factors can contribute to achieving a healthy diet. Consequently, more research is needed to demonstrate to what extent these molecules contribute to alleged neuroprotective effects of the Mediterranean Diet in the management of neurodegenerative diseases. Also, it is necessary to provide consumers with more information to guide them effectively in making wider choices of diets containing optimal levels of functional dietary components.

Food becomes fundamental in disease prevention and health promotion. This attention is contributing immensely to innovations in the areas of functional foods, nutraceuticals, phytomedicine, and molecular nutrition. New innovations in life sciences and in agri-food research have accelerated the need to ensure global food security. The solution to some health problems could be obtained in this way, if developed in a suitable scientific research and medical environment.

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Conflict of Interest

The Authors declare that there is no conflict of interest.

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