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Effects and medical application of plant-origin polyphenols: A narrative review

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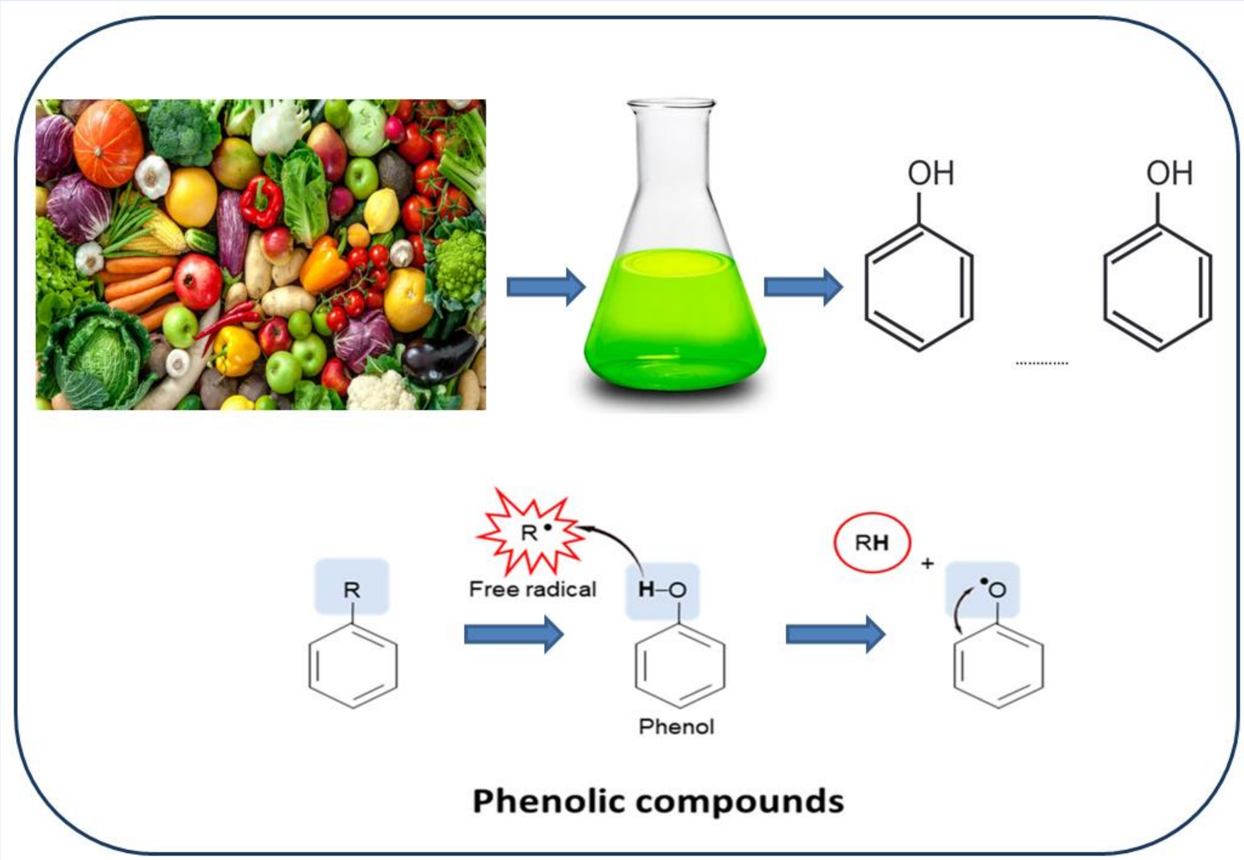
Submission date: July 15th, 2024; **Acceptance date:** August 24th; **Publication date:** August 30th, 2024

Please cite this article as: Janigashvili G., Chkhikvishvili I., Ratian L., Maminaishvili T., Chkhikvishvili D., Sanikidze T. Effects and medical application of plant-origin polyphenols: A narrative review. *Bioactive Compounds in Health and Disease* 2024; 7(8): 375-385. DOI: https://doi.org/10.31989/bchd.v7i8.1414

ABSTRACT

The impact of oxidative stress in the pathogenesis of various diseases is well known. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the ability of a biological system to detoxify these reactive intermediates or repair the resulting damage. Polyphenols, a diverse group of compounds with antioxidant properties, help reduce damage by ROS. They are abundant in fruits, vegetables, tea, coffee, wine, and other plant-based foods. The mechanisms of their antioxidant activity are related to their ability to regulate cellular signaling pathways, metal chelation, and mitochondrial protection, while modulating antioxidant enzyme activity and exhibiting anti-inflammatory effects. Polyphenols can also reduce oxidative stress through ROS scavenging, direct neutralization, or enhancing antioxidant defenses within cells. It has been established that polyphenols derived from plant compounds do not harm the metabolism of normal cells, but are involved in modulating the metabolic pathways of diseased cells, which is related to their high redox sensitivity. Incorporating polyphenol-rich foods into the diet is beneficial for maintaining overall health and reducing the risk of oxidative stress-related diseases. Researchers are exploring the therapeutic potential of polyphenols as dietary supplements or functional foods in medical applications. This review discusses the origin, structure, benefits, and application of plant polyphenols in medicine and the food industry.

Keywords: biologically active compounds, polyphenols, oxidative stress, antioxidant activity, functional food.



INTRODUCTION

The role of reactive oxygen species and other oxidants in causing various diseases is well established. ROS interact with biologically important molecules (DNA, lipids, proteins) to promote changes in DNA, cell damage, lipid and protein oxidation, and initiate oxidative stress [1]. An antioxidant protection system of the human body provides stabilization and inactivation of free reactive oxygen species (ROS), preventing DNA mutation and cell death in addition to regulating aging processes [2]. However, a "Deficiency" of endogenous enzymatic and non-enzymatic antioxidant systems can lead to oxidative stress, and the development of cancer, atherosclerosis, rheumatoid arthritis, and neurodegenerative diseases [3, 4]. Thus, natural antioxidant compounds can potentially be used for preventing and treating various diseases, and maintaining human health [5, 6, 7].

Long-term use of antioxidant therapy is effective for treating and preventing various pathological processes [5, 6, 7]. Observations have shown that antioxidant therapy normalizes cellular and tissue metabolism, and reduces inflammation, which leads to a significant decrease in the concentration of immunoglobulins, circulating immune complexes, blast-transformed form of lymphocytes in the blood, as well as the activity of lysozyme and complement [8, 9, 10], and other homeostasis indicators. Studies have also demonstrated of how antioxidant therapy aids in the correction and prevention of lipid peroxidation during chronic inflammation.

Biologically active exogenous compounds with antioxidant properties can directly inactivate free radicals and restore the activity of endogenous antioxidants, which supports the suppression of free radical oxidative processes and the prevention of oxidative stress. However, synthetic antioxidant compounds used in medical practice are often unsuccessful due to their instability, severe side effects, or low absorption/bioavailability in living tissues [11].

PLANT-ORIGIN POLYPHENOLIC COMPOUNDS

Plants synthesize a wide range of phytochemical compounds. Among them, essential polyphenols are defined as organic substances with one or more phenolic units containing hydroxyl groups in aromatic rings. The chemical properties polyphenols and effectiveness of polyphenols depend on their chemical structure, number of phenolic rings in the molecule, and number of hydroxyl groups in the aromatic rings [12, 13]. In addition, the biological activity of plant-based phenols varies depending on the plant yield, processing methods, storage conditions of the processed product, the possibility of interaction between phenolic compounds and other natural compounds or artificial additives, as well as the external environment - the physiological state of the patient's body (factors such as gender, age or health status, habits, lifestyle) [13].

Based on their fundamental chemical structure, polyphenols can be divided into flavonoids, phenolic acids, and non-flavonoid polyphenols (Figure 1).

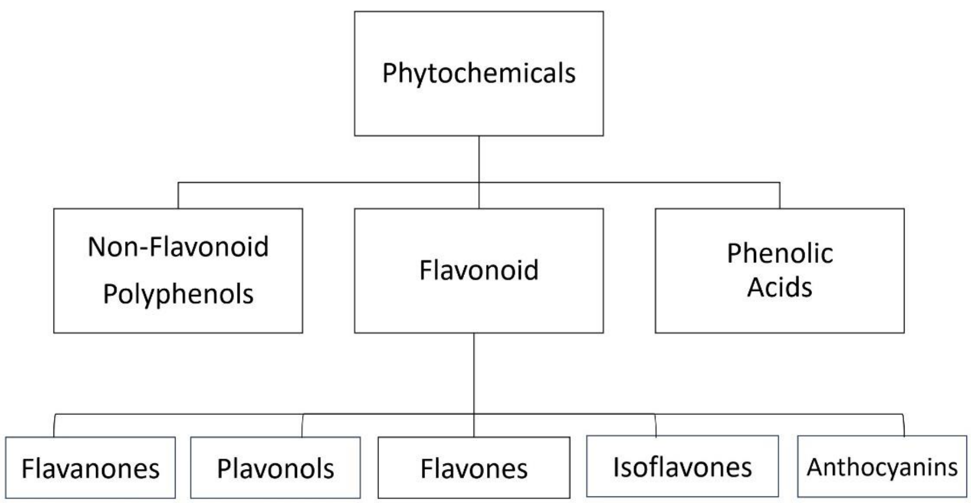


Figure 1. Scheme of polyphenolic compounds

Plant phenolic acids usually occur in the form of complexes with other polyphenols or saccharides. According to their molecular structure, they are divided into two main groups: derivatives of hydroxycinnamic and hydroxybenzoic acids. Gallic acid (derivative of hydroxybenzoic acid), ellagic acid (derivative of gallic acid), and caffeic acid (derivative of hydroxycinnamic acid) and their derivatives - chlorogenic, neochlorogenic, rosemary, etc. - are of greatest interest to scientists and practical pharmacologists. The biological activity of phenolic acids primarily depends on their absorption, assimilation, duration of decay after entering the bloodstream, bioavailability, and level of metabolic activity. Numerous epidemiological and experimental data indicate a protective role of phenolic acids in the treatment of neurodegenerative, and cardiovascular diseases, as well as cancer, diabetes, various inflammatory processes, etc. [14].

Non-flavonoid polyphenols regulate bone homeostasis by reducing oxidative stress and modulating epigenetic mechanisms through deacetylases and microRNAs. They support the enhancement of osteoblast differentiation and activity, inhibit osteoclast differentiation and activity, promote bone deposition, and inhibit its resorption [15]. Phenolic acids and non-flavonoid polyphenols are commonly used in the treatment of osteoporosis.

Flavonoids are the most important group of antioxidant compounds in plants, with over 6,000 identified molecules. Flavonoids are classified into different families based on structural changes in the rings, such as the degree of hydrogenation, hydroxylation, and oxidation. These families include flavonols, flavones, flavanones, catechins, leucoanthocyanidins, and anthocyanins (Figure 1). These compounds, secondary metabolites of plants, are characterized by their multifunctional activities and are involved in important metabolic processes for cell viability, such as growth, proliferation, and protection against ultraviolet radiation [16].

Activity of polyphenols: For centuries, people have used herbal medicines to treat various diseases [5]. In recent years, there has been an increase in the use of herbal remedies in medicine, despite the rapid development of modern medicine and pharmacology. Thus, herbal medicines play an important role in the contemporary healthcare system.

In addition, traditional medicine is used for its therapeutic and prophylactic purposes, especially in developing countries. Propolis extract, citrus extracts (hesperidin), red grapes, and tea polyphenolic compounds have been shown to neutralize free radical oxidation, reducing the risk for various acute and chronic diseases, including diabetes mellitus, hyperthyroidism, obesity, cancer, aging, atherosclerosis, cardiovascular diseases, immunosuppression, neurodegeneration, radiation sickness and others [7, 17, 18, 19, 20, 21, 22]. Although most medicinal plants have not been studied for toxicity, it is generally recognized that herbal remedies with antioxidant properties are safer than synthetic analogs [11].

In addition, it is well established that these compounds have a differentiated effect on normal and diseased cells - they modulate the metabolic pathways of diseases and are completely harmless to the metabolism of normal cells. This is due to their high oxidation-reduction sensitivity, which allows them to respond to the slightest changes in the internal oxidation-reduction status of tissue cells, making it possible to regulate oxidative metabolism and the activity of the body's detoxification system [27, 28, 29]. Polyphenols can donate electrons to neutralize ROS, reducing damage on cellular components. Polyphenols can also chelate transition metal ions (e.g., iron and copper) involved in the generation of ROS through Fenton reactions and increase the expression and activity of endogenous antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase. These enzymes help detoxify ROS and maintain cellular redox balance.

All polyphenol representatives are characterized by signal-transmitting ability between cells and impacting gene expression [7, 23, 24, 25, 26].

Polyphenols are found in fruits, vegetables, herbs, spices, tea, and other plants available in Georgia. They are characterized by antiviral, anti-inflammatory, antioxidant, and apoptosis regulatory activities [24, 25, 26, 27, 28]. Polyphenols can specifically protect the mitochondria from oxidative damage, support cellular energy production, reduce ROS production during mitochondrial dysfunction, and modulate signaling pathways involved in cellular responses to oxidative stress. Polyphenols can mitigate inflammatory responses accompanied by ROS generation, indirectly reducing oxidative stress.

One example of a natural non-flavonoid polyphenol that exhibits several beneficial properties is resveratrol. Several studies demonstrated that plant extracts containing resveratrol significantly reduced levels of TGF-β and blocked its signaling pathways (Smad3/4, p-Smad3/4, CTGF, and p-ERK1/2)., Resveratrol was also shown to prevent inflammation, oxidation, and collagen deposition [33, 34, 35] as well as maintain a therapeutic effect on pulmonary fibrosis (by suppressing the TGF-β/Smad signaling pathway) and inhibiting cell apoptosis. In addition, Resveratrol has antiviral activity (MERS-COV virus replication), with antiviral drug development potential [16, 36, 37, 38]. Therefore, the presence of resveratrol is important for functional food development.

Activity of flavonoids: Citrus fruits, especially their peel, are rich in flavonoids. These fruits play an integral role in epigenetic mechanism modulation, estrogen signaling transduction, cell death regulation through induction of apoptotic signaling pathways, and inhibition of tumor growth, tumor cell invasion, and metastasis formation [39]. For example, hesperidin, a flavonone found in citrus fruits, has therapeutic use due to itsantioxidant, anti-inflammatory, and immunomodulatory properties. Numerous clinical studies, both in vivo and in vitro, have demonstrated that hesperidin contributes to immunomodulation by reducing inflammatory markers such as TNFα, IL-1β, IL-4, IL-6, IL-8, IL-12, ICAM-1, and VCAM-1. Hesperidin inhibits enzymes and their expression, including MAPK/ERK, phospholipase A2, lipoxygenase, HMG-CoA reductase, COX-2, and iNOS. Other citrus compounds, such as naringenin, and hesperidin have also been identified as having potential anticancer properties, particularly for breast cancer.

Hesperidin also exhibits beneficial properties, in combination with other flavonoid compounds found in citrus fruits. For example, with naringenin, quercetin, and rutin, hesperidin protects against skin damage and demonstrates cardio--, neuro-, and nephroprotective properties. Naringenin also inhibited the SARS-CoV-2 major protease [41] by forming a protonated H-bond with the active site of the amino acids chain [42]. Hesperidin and hesperetin can boost antiviral defense by enhancing the expression of the interferon transcription regulatory factor and activating the interferon-stimulated response element. Hesperidin is effective against human rotavirus, the causative agent of diarrhea in infants. This is through inhibition of the influenza virus replication in vitro and decreases the number of infected cells. Hesperidin has also been found to inhibit various sexually transmitted pathogens, including Neisseria gonorrhoeae, Chlamydia trachomatis, herpes simplex virus-2, and human immunodeficiency virus. Importantly, hesperidin had no toxic effects on the host cells or the growth of normal vaginal lactobacilli. In addition, hesperidin demonstrated in vitro activity against the canine distemper virus and maintained protective effects in mice infected with encephalomyocarditis virus and Staphylococcus aureus [40]. Other studies have shown that hesperidin binds to the viral (S) protein receptor and ACE-2 (PD-ACE-2) peptidase domain [43, 44, 45, 46], reducing angiotensin-converting enzyme receptor activity. Naringenin, hesperetin, and hesperidin also attenuate inflammatory reactions, preventing LPS production of pro-inflammatory cytokines (COX-2, iNOS, IL-1β, and IL-6) in macrophage cells [47] and reducing cytokine shock in patients with severe COVID-19 disease. Hesperidin is also known to reduce histamine release from mast cells [39], alleviate coughs, and improve digestive systems. Therefore, hesperidin and other flavonoids have therapeutic potential in medical applications.

Additionally, polymethoxylated flavonoids can be found in citrus fruits. Polymethoxylated flavonoids are secondary metabolites with a basic structure derived from the flavone nucleus. Replacing two or more hydroxyl groups on the A and B rings of the flavone nucleus with two or more methoxyl groups reduces their polarity and facilitates their penetration through cell membranes. Polymethoxylated flavonoids have anti-inflammatory properties, thus helping to prevent, metabolic, cardiovascular, neurodegenerative, and oncological diseases [47]. Polymethoxylated flavones, along with other citrus flavonoids. also have anti-COVID-19 activity [42].

Among flavonols, the most common and studied representative is quercetin. They are found in fruits, green vegetables, broccoli, olive oil, onions, buckwheat, nuts, seeds, flowers, bark, green tea, red grapes, red wine, apples, dark cherries, and berries such as blueberries and cranberries [29, 48]. Quercetin is a widely used bioflavonoid for the treatment of metabolic and inflammatory processes. It is characterized by gastroprotective, immunomodulatory, antidiabetic, anti-obesity, antiallergic, antiviral, and anti-infective effects. Quercetin also has anti-atherosclerotic, anti-hypercholesterolemic, anti-hypertensive, and cardioprotective effects due to its vasodilating activity, Quercetin and its related metabolites may also protect against environmental sources of free radicals, such as smoking [49].

Catechins are abundant in tea, particularly green tea, and some fruits. The most common representatives of catechins are several stereoisomers of epicatechin, epigallocatechin, and epigallocatechin gallate. Regarding chemical structure, catechins are typically not glycosylated and can provide polymerization and esterification, leading to the formation of tannins. In addition, studies show that catechins can inhibit oxidative stress and reduce tissue damage by promoting the activation of antioxidant enzymes, like glutathione peroxidase and glutathione reductase. Catechins can also reduce inflammatory response by regulating the infiltration and proliferation of immune cells (neutrophils, epithelial cells, macrophages, and T lymphocytes). Anti-inflammatory properties of catechins are revealed through the activation/deactivation of inflammation- and oxidative stress-related cell signaling pathways, such as nuclear factor-kappa B (NF-κB), mitogen-activated protein kinases (MAPKs), signal transducer, and the activator of transcription 1/3 (STAT1/3) pathways [53]. Therefore, catechins are anti-atherosclerotic, anti-diabetic, anti-obesity (prevention of metabolic syndrome), anti-inflammatory, anti-carcinogenic anti-bacterial, and anti-viral. [9, 50, 51, 52, 53]

Polyphenols in the medical and food industries: Alongside their many biological effects, polyphenols are also important in physiology and medicine, and in functional and specialized food products for therapeutic and preventive nutrition [54]. There are growing concerns regarding changes in eating habits over the last century that contribute to the development of obesity, atherosclerosis, and cardiovascular disease. Therefore, there are many efforts to study biologically active substances, like polyphenols, in traditional food plants to create functional foods (i.e., a food additive) and address this problem while considering the diversity of dietary preferences and behaviors. For example, polyphenol-rich fruits, vegetables, tea, coffee, and red wine, are the subject of intensive scientific research in Georgia. Thus, food additives containing polyphenol compounds are produced in Georgia for their prophylactic and therapeutic effects (antiviral, antioxidant, immunomodulatory, anticoagulant, antifibrinolytic) [18, 20, 21, 26, 60-61].

The novelty of this work: The novelty of our review lies in the analysis of the latest research results concerning the use of bioactive substances of plant origin in the prevention and treatment of various diseases. The review will contribute to the development of new and effective therapeutic strategies using the preventive and therapeutic potential of traditional food plants, their use in the form of food products, as well as food additives, in the healthcare system to maintain public health.

CONCLUSION

In summary, among the wide range of phytochemicals synthesized in plants, polyphenols, (organic substances with one or more phenolic units, containing hydroxyl groups in aromatic rings), have been shown to have particularly high bioactivity.

Polyphenol compounds –aid in modulating metabolic pathways of diseased cells, while maintaining normal cell metabolism. This is due to their high redox sensitivity, which regulates the oxidative metabolism and activity of the body's detoxification system. All polyphenols are characterized by their signal-transmitting ability between cells, which impacts gene expression. Therefore, these actions by polyphenols contribute to their antioxidant, anti-inflammatory activity, and apoptosis-regulating properties.

In this regard, the study of biologically active substances contained in traditional food plants and the use of their preventive and, possibly, therapeutic potential in food additives is very promising. Further research focusing on the identification of compounds with novel effective pharmacological properties and their respective molecular mechanisms of action is needed [62].

List of Abbreviations: DNA, deoxyribonucleic acid; miRNAs, microRNA - small, single-stranded, non-coding RNA molecules containing 21 to 23 nucleotides in plant; ROS, reactive oxygen species; TGF-ß, transforming growth factor ß; Smad, a family of structurally similar proteins that are the main signal transducers for receptors of the superfamily TGF-ß, CTGF, connective tissue growth factor; $ERK_{1/2}$, extracellular signal-regulated kinase ½; MERS-COV, middle east respiratory syndrome coronavirus; TNFα, tumor necrosis factor α; IL, interleukin; ICAM-1 - intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion molecule 1; MAPK, mitogen-activated protein kinase 1; HMG-CoA-3, hydroxy-3-methylglutaryl coenzyme A; COX-2, cyclooxygenase-2; iNOS, inducible nitric oxide synthase; SARS-CoV, severe-acute-respiratory-syndrome-related coronavirus; ACE-2, angiotensin-converting enzyme-2; PD-ACE-2, angiotensin-converting enzyme-2 peptidase domain; LPS, lipopolysaccharide; COVID-19, coronavirus disease-19; NF-κB, nuclear factor-kappa B; STAT1/3, signal transducer and the activator of transcription 1/3.

Authors' Contributions: The manuscript was written with contributions from all the authors. All authors have approved the final version of the manuscript.

Conflict of Interest: The authors declare no potential conflicts of interest related to this study.

Funding: This manuscript was financed in frames of PhD program of Tbilisi State Medical University (Georgia).

Acknowledgment: The author wishes to extend heartfelt gratitude to Tbilisi State Medical University for support of this manuscript.

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