Effect of polyphenol secondary metabolites on oxidative stress and inflammatory responses associated with aging diseases

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ABSTRACT:

Several mechanisms are responsible for regulating the process of aging. A rise in reactive oxygen species (ROS) and oxidative stress is usually linked to the development of age-related diseases. Evidence indicates that prolonged oxidative stress can predispose to frequent diseases such as chronic inflammation, cancer and heart diseases. Polyphenols are naturally occurring substances found in numerous fruits, vegetables, cereals, etc. They considered as one of the most abundant and widely distributed secondary metabolites of the plant kingdom. Long-term consumption of polyphenol-rich diets was confirmed for protection from as shown by earlier. Additionally, polyphenol-rich foods and beverages offer protection against certain chronic diseases, particularly type 2 diabetes and heart disease. Certain polyphenols, such as quercetin, have anti-inflammatory properties and they were also associated with lower levels of biomarkers of muscle injury and inflammation. Flavonoids were shown to slow memory problems and the progression of Alzheimer's disease. Antioxidants such as plant polyphenols have been proposed for cancer prevention and/or treatment. Dietary benefits are attributed in part to polyphenols, which have antitumor properties in both animal models and humans. Resveratrol (RV), a polyphenol found in blueberries, cranberries, wine almonds, and red grapes, has anti-inflammatory and anti-cancer properties and was shown to reduce cancer cell glycolytic metabolism and reduce intracellular ROS levels.

Keywords: aging process, reactive oxygen species, oxidative stress, anti-inflammatory.

الخلاصة: هناك مجموعة متنوعة من العمليات المسؤولة عن تنظيم عملية الشيخوخة ، أي زيادة في أنواع الأكسجين التفاعلية (ROS) والإجهاد التأكسدي مرتبط بالأمراض المرتبطة بالعمر. تشير الدلائل إلى أن الإجهاد التأكسدي المطول يمكن أن يكون عاملاً مسببًا له علاقة بالعديد من الأمراض. البوليفينول عبارة عن مواد موجودة بشكل طبيعي في العديد من الفواكه والخضروات والحبوب وما إلى ذلك ، وهي واحدة من أكثر فئات المنتجات الطبيعية وفرة وتوزيعًا على نطاق واسع في المملكة النباتية. وُجد أن الاستهلاك طويل الأمد للأنظمة الغذائية النباتية الغنية بالبوليفينول يساعد في توفير الحماية من السرطان في دراسات سابقة. بالإضافة إلى ذلك ، توفر الأطعمة والمشروبات الغنية بالبوليفينول الحماية من بعض الأمراض المزمنة ، وخاصة مرض السكري من النوع 2 وأمراض القلب. تحتوي بعض البوليفينول ، مثل كيرسيتين ، على خصائص مضادة للالتهابات ، كما أنها مرتبطة بمستويات أقل من المؤشرات الحيوية لإصابة العضلات والالتهابات. وقد ثبت أن مركبات الفلافونويد تبطئ مشاكل الذاكرة وتطور مرض الزهايمر. تم اقتراح مضادات الأكسدة مثل البوليفينول النباتي للوقاية من السرطان و / أو علاجه.ويُعزى ذلك الى الفوائد الغذائية لمادة البوليفينول ، التي لها خصائص مضادة للأورام في كل من النماذج الحيوانية والبشر. الريسفيراترول (RV) ، بوليفينول موجود في العنب البري والتوت البري ولوز النبيذ والعنب الأحمر

، له خصائص مضادة للالتهابات ومضادة للسرطان وقد ثبت أنه يقلل من التمثيل الغذائي للخلايا السرطانية ويقلل من مستويات ROS داخل الخلايا.

الكلمات المفتاحية :عملية الشيخوخة ، أنواع الأكسجين التفاعلية ، الإجهاد التأكسدي ، مضاد للالتهابات.

INTRODUCTION:

Aging is a bio phenomenon, with a gradual loss of cellular functions and decreased tissue renewal capability in multicellular organisms, resulting in a decreased ability to resolve environmental factors. A number of mechanisms may involve in regulating the aging process, including genetic, epigenetic, and environmental factors [1]. Aging, on average, harms wellbeing, according to certain studies, a rise in reactive oxygen species (ROS) and the resultant oxidative stress is connected to age-related diseases. In reality, the antioxidant properties of natural compounds were illustrated in a variety of studies [1,2]. "Phytochemicals" is a term used to describe substances that are found in plants[2]. Polyphenols are naturally substances found in many fruits, vegetables, cereals, and other foods. Alcoholic drinks (apple, pear, cherries, grapes, and berries) for example, contain 200-300 mg of Polyphenols in every100 gram of fresh weight [1]. Polyphenols are secondary metabolites found in plants that reflect certain characteristics in food such as bitterness, astringency, color, taste, odor, and oxidative stability. They are widely found in foods and are used to defend against UV rays and pathogens[3]. Epidemiological research and related meta-analyses near the end of the 20th century strongly suggested that long-term consumption of plant polyphenol-rich diets provided some cancer protection [4].The purpose of this article is to review the health benefits of polyphenols and other phenolic found in foods focusing on their antioxidants mechanisms and the impact of this on human wellbeing and diseases associated with old age.

The consequences of oxidative stress and how it interacts with age related diseases.

The accumulation of Reactive Oxygen Species (ROS) damages mRNA and inhibits lipid/protein oxidation, resulting in a reduction in mitochondrial function and increased oxidative stress. As people age, they may experience a gradual loss in mitochondrial function and oxidative stress responses [4].

Reactive oxygen species, antioxidant balance and oxidative stress

At acceptable levels, ROS, an unavoidable byproduct of aerobic respiration, is beneficial and necessary for normal cellular responses and cell-mediated immunity. Reactive nitrogen species (RNS) may be beneficial to the body in a similar way [2]. Antioxidants are capable of neutralizing excess ROS/RNS in a normally functioning cell. "Nonetheless , overproduction of (O_2-), (•OH) (ONOO), (H_2O_2), and other reactive organisms (ROOH),($1O_2$), reactive lipid aldehydes, and reactive nitric oxide (NO), are accompanied by an antioxidant deficiency in the body Accordingly, there is enhanced oxidative damage to the body, mainly at cell constituents level (protein, lipids, and DNA)" [5]. This condition primarily promotes abnormal cell death, inflammation, and, as a result, age-related diseases. According to a study made by (Munialo CD, 2019), antioxidants supplementation prove effectiveness in replenishing low levels of endogenous antioxidant evidence by scavenging reactive oxygen species (ROS/RNS) [6]. Exogenous supplements (minerals, vitamins, organ sulfur compounds, carotenoids, and polyphenols) have been shown to improve health and preserve antioxidant resistance, resulting in a long and healthy life [7].

Polyphenol's History

Polyphenols have historically piqued the interest of plant scientists because they play different roles in plants and are classified as secondary metabolites. Plants are protected from environmental stresses such as drought, by producing certain phytochemicals or metabolites. UV light both protects against pests and adds color to attract them[3]. Hesperidin, flavonoid, in the 1930s was suggested to be labeled as a vitamin (vitamin P), in the nineties; polyphenols came to be recognized as antioxidants [8]. However, the fact is much more complex, and biological processes involve complicated interactions with molecular pathways. As a result, much progress has been made in the last two decades. Polyphenol-rich foods and beverages offer protection against certain chronic diseases, particularly type 2 diabetes, hypertension and heart disease[9].. They have a limited commercial application as nutraceuticals due to their weak solubility, instability when exposed to light, heat, and alkaline environments, and low consistency [1].

Polyphenol classification number

Polyphenols are one of the most abundant and widely distributed natural product categories in the plant kingdom. There are currently over 4000 flavonoids with recognized structures discovered, in addition to over 8000 phenolic compounds [10]. Polyphenols are categorized into certain classes based upon their, Origin, chemical structure, and biological functions [11].

They are divided into four categories [12]:

Phenolic acids: They account for nearly one-third of the polyphenolic chemicals in the diet and can be found in any plant material, though they are especially abundant in sour fruits. Ferulic, caffeic, gallic, and phenolic acids are all examples of common phenolic acids.

Flavonoids: The most common polyphenols found in healthy diets are flavonoids, which all have the same basic structure: aromatic rings (only two) fused by carbon atoms (three atoms)to form an oxygenated heterocyclic.

Stilbenes: These are a form of supplement from the diet, that contains stilbenes, a methylene bridge with two carbon atoms that connect two phenyl groups. Antifungal phytoalexins, formed as part of response against infection, constitute the predominant stilbenes in plants.

Two cinnamic acids: residues dimerize to form a 2, 3-dibenzylbutane structure in lignans, which are phenolic compounds.

Polyphenols in nature.

Polyphenols can be present in leaf tissue, the bark layer, flowers, and fruits of almost all plant families. Phenolic compounds exist in plants at the tissue, cellular, and subcellular levels. Cell walls contain insoluble phenolic compounds, while the plant cell vacuoles contain soluble phenolic compounds. Also, it can be found in a variety of plant products, including tomatoes, cereals, fruit juices, tea, and wine. A variety of factors influence plant polyphenol content, including harvest ripeness, storage, and environmental factors (soil type, sun exposure, rainfall) [13, 14].

Polyphenols are present in the form of flavanones and isoflavones, on the other hand, foods may contain complex polyphenols [14] as shown in table-1.

Table (1): the content of polyphenols in food and beverages [14].

Chemical class	Most common examples	Rich sources
Flavanols	Catechins Gallo-catchines	Tea, cocoa ,apples ,broad bean
Flavanones	hesperidin	Citrus fruit
Flavonols	Quercetin, rutin	Tea, apples, onions
Hydroxy-cinnamic Acid	Chlorogenic acids (caffe-oylquinic acids)	Coffee, chicory, artichoke plum, pears
Anthrocyanin	cyanidin	Beery fruits

Polyphenols and Diseases Caused by Oxidative Stress (OS)

Evidence indicates that prolonged oxidative stress (OS) can be an etiological factor involved in several diseases, including heart disease, diabetes, and neoplastic diseases. Several factors contribute to the excessive generation of free radicals, including diet, lifestyle habits, and environmental factors including pollution and radiation [2].

Molecules possessing one or more unpaired electrons are known as free radicals like nitric oxide, superoxide, and hydroxyl radicals. Oxidative Stress can also be caused by the body's natural immunological response. Mild inflammation is caused by this type of oxidative stress, and it goes away after the immune system overcomes infection or an injury is resolved [5]. Excessive oxidative stress has been shown to hasten age. Physical activity-induced OS, for example, may have well, regulating consequences on the body. Polyphenols protect against exhaustion, inflammation, and tissue damage caused by intense exercise [17]. Exercise promotes the development of free radicals, which can result in transient oxidative stress in the muscles. Free radicals generated during physical activity, on the other hand, regulate the growth of tissues and stimulate the development of growth factors. Mild OS can protect against infection and disease. According to a report, OS slowed the spread of HIV [15]. Long-term OS, on the other hand, has detrimental effects on cells, proteins, and DNA. This can accelerate aging and precipitate many diseases

Oxidative stress and chronic inflammation

Infections and accidents activate the immune system. When fighting off invading germs, immune cells called macrophages create free radicals. These free radicals can cause inflammation by damaging healthy cells. In most cases, inflammation subsides after the immune system has done its job, removes the infection [7]. Oxidative stress, on the other hand, can activate the immune response, which produces more free radicals, aggravating Oxidative Stress even more, effectively bringing about a vicious cycle. The biosynthetic pathway for prostaglandins (PGs) is intimately linked to the relationship between oxidative stress and chronic inflammation [12]. Cyclooxygenase (COX) is an important enzyme responsible for the synthesis of prostaglandins (PGH2) from arachidonic acid. As shown in the figure-1, the conversion of (PGG2) to (PGH2) generates reactive species[16].

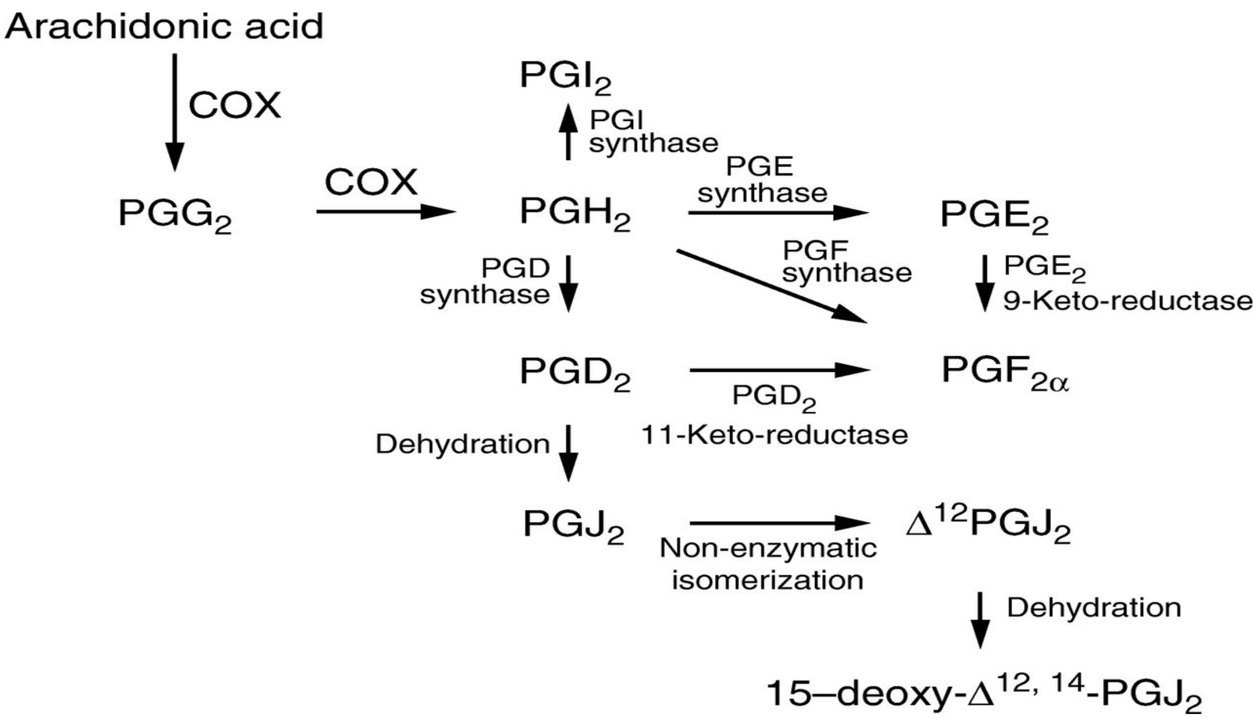

Figure (1): Formation of reactive oxygen species by prostaglandin pathway [16].

Protective effects of polyphenols on exhaustive exercise induced fatigue, inflammation and tissue damage

The tea polyphenols allowed the rats to stay active for longer than the non-polyphenol-treated rats. They also had lower levels of biomarkers of muscle injury and inflammation [17]. Lignans are a form of polyphenol found in highest concentrations in virgin olive oil, flaxseed, and whole grain rye flour. A study reported that higher urinary concentrations of lignans were linked to a lower degree of inflammation. This is important since chronic inflammation that contributes to several diseases, including cancer and heart disease, has been connected to it [18].

Vascular diseases

Oxidative stress can cause aging, genetic disorder, conventional risk factors, and external conditions, especially in vessels where (NADPH), NOX (Nitrogen oxide) and uncoupled NOS (Nitric oxide synthase) are the primary oxidative stress sources. A small increase in net ROS at physiological levels may trigger protective effects via redox signaling, resulting in an increased anti-oxidative potential for improved anti-oxidative capacity [5]. The cellular damage and endothelial dysfunction occur when ROS production exceeds the ability of the body's anti-oxidative defenses, contributing to coronary artery disease [15]. Ischemic stroke during a myocardial infarction (MI) results in a loss of functional myocardium and, eventually, heart failure which can also be caused by other factors, such as primary cardiomyopathy or diabetes. Specific mechanisms, such as receptor-induced NOX2 (Nitrogen oxide2)

Activation and mitochondrial redox mismatch, because increased cardiac oxidative stress. As a result, mitochondrial NADPH(Nicotine amide adenine dinucleotide Phosphate) oxidation produces hydrogen peroxide (H2O2), which causes contractile dysfunction, arrhythmia, and ultimately maladaptive cardiac renovating via atrophy and cell death [19].

Flavonoid-rich cocoa's cardio protective effects

Polyphenols, an essential component, account for up to 18% of the total weight of cocoa. Phenolic compounds with the greatest abundance in cocoa and cocoa products are flavonoids such as epicatechin, catechin, and proanthocyanidins. Their flavonoid content is greater than other polyphenol-rich foods [9]. Endothelial NO synthase (eNOS) is activated by all polyphenols, regardless of their source, resulting in NO(Nitrogen oxide) output that activates guanylate cyclase in smooth muscle cells and platelets, increasing cyclic guanosine monophosphate (cGMP). Because of the subsequent inhibition of calcium flux and reduction in cellular calcium composition, smooth muscle cell relaxation and platelet aggregation are inhibited. Furthermore, cGMP increases the formation of cyclic adenosine monophosphate (cAMP), which also stimulates the prostacyclin [20]. Prostacyclin functions as a vasodilator in a synergistic manner.NO contribute to thrombosis defense by increasing NO levels. Furthermore, prostacyclin's ability to lower plasma leukotrienes enhances its anti-inflammatory and vaso-protective properties [21]. Following ingestion of cacao and dark chocolate, a sequence of incidents occurs involving NO and cGMP-induced dilatation of vessels, and anti-inflammatory effect mediated by prostaglandins occur [22].

In reality, cocoa polyphenols lower NADPH levels (which produces O2, which scavenges NO). As a result, it inhibits the increase of NO levels[23]. Platelets are yet another significant goal of polyphenol, present in high levels in cocoa. First and foremost, platelets will liberate NO under the impact of flavanols, resulting in vasodilation [24]. For cocoa-mediated platelet aggregation inhibition, Thromboxane A2 (TXA2) formulation must be reduced and TXA2 receptors must be antagonized [25].

The Health Benefits of Polyphenols on CNS and Behavioral patterns.

Polyphenol's effects on the CNS were extensively researched including both experimental animals and humans. Flavonoids found in Ginkgo biloba were shown to slow memory problems and the progression of Memory loss (Alzheimer) [26]. Flavonoids inhibit protein kinase while increasing the representation of brain-derived neurotrophic factor (BDNF), a key component that promotes neurogenesis, synaptic progression, and neuron ability to survive in brain regions involved in learning and memory, such as sub ventricular regions[27]. Other mechanism depends on NO production, which causes dilatation of blood vessels and enhanced cerebral blood flow and circulatory in the CNS and peripheral nervous system[28]. Increased blood flow will supply oxygen and nutrients to nerve cells, as well as removing waste compounds from the brain and encouraging angiogenesis in the hippocampus[29].

The role of dietary polyphenols in the prevention of diabetes mellitus.

Many studies have found that oxidative stress contributes to the representation and health of diabetic complications[30]. Polyphenols can affect glycemic control in different ways, including inhibiting glucose metabolism and intestinal absorption, stimulating pancreatic–cell insulin secretion, modifying glucose transport from the liver, triggering insulin receptors and glucose absorption in insulin-sensitive body tissue, and modulating hepatic glucose output [31].

Curcumin as a possible diabetes mellitus treatment and prevention agent:

Curcumin is a polyphenolic compound extracted from the Indian spice turmeric (Curcuma longa), a ginger-related plant. The intestinal microbiota degrades curcumin as well as other polyphenols, resulting in very little or no native curcumin in circulation. Several in vitro and in vivo studies, nevertheless, have demonstrated that these compounds can have anti-diabetic properties, implying that tissue effects are associated with these compounds or their degradation products [30]. At the same time, curcumin'ˢ polyphenols(C/local P's) intestine activities may cause changes in the microbial flora's makeup. As a result, the changed flora may have an impact on C/P) Curcumin and other polyphenols)metabolism. Short-chain fatty acids stimulate GLP-1(Glucagon-like peptide-1)release, which increases insulin release and alters intestinal wall penetrability, resulting in improved metabolic control [30].

Polyphenols have a cancer-protective effect.

Cancer is one of the world's most serious diseases. In 2018, 9.6 million people died from cancer, according to the World Health Organization (WHO). However, 30% of cancers are preventable, and most of the cancer types, such as breast, colon cancer, and cervical cancer, can be cured if diagnosed and treated early. Oxidative stress is among the most major factors that lead to cancer [32]. Many researchers have indicated that a diet rich in antioxidants, in particular, may aid in cancer prevention[33]. Dietary benefits are attributed in part to polyphenols, which have antitumor properties in both animal models and humans[34]. Many dietary polyphenolic compounds were shown to possess anticancer activity, including Methylation of DNA, histone acetylation phase, and gene transcription, mRNA-regulated cancer stem cell biology, and the initiation of premature senescence in tumor cells[35]. According to evidence from cancer epidemiology and experimental efforts, polyphenols have a promising future as epigenetic activators and cancer stem cell metabolic processes regulators in modern anticancer approaches[36]. Curcumin possesses anti-inflammatory and antioxidant properties that have been linked to a variety of health benefits, including cancer prevention. Curcumin's long-term action on the liver of lymphoma-affected mice prevents cancer by increasing phase-II antioxidant enzymes, restoring tumor suppressor p53, and modulating inflammatory mediators such as interleukin-6[36]. Resveratrol (RV) has anti-inflammatory and anti-cancer properties. It can influence cell proliferation, apoptosis, angiogenesis, and tumor metastasis via modulating signaling pathways[37]. Due to its antioxidant activity and effects on glucose metabolism, RV is also gaining popularity.

CONCLUSION:

Polyphenols are bioactive substances found in a variety range of fruits, vegetables, and drinks. They include numerous phenol structural units and have anti-inflammatory, anti-diabetic, antioxidant, anti-tumor, and antihypertensive characteristics, and their consumption at a sufficient level may protect against certain diseases. They have a limited commercial application as nutraceuticals due to their weak solubility, instability when exposed to light, heat, and alkaline environments, and low consistency. Polyphenols are important option for the management of noncommunicable diseases. Their bioavailability, biochemical detection, particular molecular targets, ability to interact, and toxic effects are all factors to consider. The remaining outstanding challenges must be actively managed.

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