World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 6.129

ROLE OF PHENOLIC COMPOUNDS IN PREVENTION AND MANAGEMENT OF HUMAN DISEASE

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Article Received on 22/02/2023 **Article Revised on 12/03/2023** **Article Accepted on 02/04/2023**

ABSTRACT

Phenolic compounds represent a group of molecules and its functions in the growth and development with a defense mechanism in plant. It includes pigments, signaling molecules, and flavors which will protect the plant against insects, fungi, bacteria, and viruses and plays a role to attract or repulse them. Inflammation is a natural protective mechanism that occurs when the body's tissue homeostatic mechanisms are disrupted by biotic, physical, or chemical agents. The immune response generates pro-inflammatory mediators, but excessive output, such as chronic inflammation, contributes to many persistent diseases. Some phenolic compounds work in tandem with nonsteroidal anti-inflammatory drugs (NSAIDs) to inhibit pro-inflammatory mediators' activity or gene expression, including cyclooxygenase (COX). Various phenolic compounds can also act on transcription factors, such as nuclear factor-κB (NF-κB) or nuclear factor-erythroid factor 2-related factor 2 (Nrf-2), to up-or down regulate elements within the antioxidant response pathways. They were having many health benefits like UV screens, attractants, signal compounds, and other response chemicals from different types. As per the human physiology, they are vital in protection and play an important role in prevention and treatment of many chronic diseases. It also acts as antioxidant, antiseptic, anti-proliferative activities, antidiabetic, anti-inflammatory and anti-aging. They are useful to eat such plant foods that contain high antioxidant content, which can hamper the incidence of certain chronic diseases, such as cardiovascular diseases, diabetes and cancers, through the management of oxidative stress. This study also discusses current issues and potential prospects for the therapeutic application of phenolic compounds to various human diseases.

KEYWORDS: Phenolic compound; Diabetic mellitus; Cardiovascular disease; Antioxidant, Health benefit.

INTRODUCTION

Grains, mainly cereals and legumes, are important in every diets of human in any part of the world. They are rich in diverse nutrients and phytochemicals, and possess manifold bioactivities, such as antioxidant, antidiabetic, and anticancer effects.[1-3] Phenolic compounds [PC] are distributed everywhere in most of the plant tissues which includes the parts such as roots, stems, fruits, seeds, leaves, etc.[4] There are more than 8000 individual plant with great chemicals isolated, structural variability and nearly 200000 were identified with diverse structures.[5] and classes from higher plants around the planet. They are classified as primary metabolite and secondary metabolite.[6] The primary metabolite is required for cell nourishment, such as carbohydrates, proteins, fatty acids and nucleic acids. The secondary metabolite is essential to plant survival which directly involved in photosynthetic or respiratory metabolism. As differentiated from primary metabolite, the chemicals and structures of secondary metabolite are responsible for plant defense. They also protect the plant from oxidants and ultraviolet radiation and also act as attracting pollinators or animals for seed dispersion and signal compounds.[6-8]

The secondary metabolite is classified according to their biosynthetic routes and structure; they are divided into three major groups: (1) flavonoids, allied phenolic, and polyphenolic compounds; (2) terpenoids, and (3) nitrogen-containing alkaloids and sulfur-containing compounds. These compounds are linked to primary metabolite by biosynthetic enzymes and building blocks.[8] Phenolic compounds (flavonoids, allied phenolic, and polyphenolic compounds) are one among the secondary metabolites more cosmopolitan in plants. The shikimate, pentose phosphate and phenylpropanoid pathways are extract from plants. These compounds perform an important role in the growth and reproduction of plants, giving protection against pathogens and predators. In vegetables and fruits, PC contribute to color and sensory characteristics.[8,9]

Phenolic compounds

The compounds that have one or more hydroxyl groups connected straightway to the ring of an aromatic. The whole category is based on the arrangement of phenol. In phenols, the hydroxyl group is linked to a chain of carbons which are alike to alcohols of aliphatic structures. Due to the existence of the aromatic ring, the phenolic hydroxyl group is affect. The hydrogen of the phenolic hydroxyl is unstable caused by the aromatic ring that builds the phenols as a weak acid.[10] Its structure consists of an aromatic ring that contains 1 or more hydroxyl substituent's. It may be classified into simple phenolic molecule and extremely polymerized compounds. The PC occur naturally is associated with one or more phenolic groups when combine with mono- and polysaccharides. In addition, they also can be linked to esters and methyl esters. They have a wide range in structure diversity that occurs in nature. More than 8000 structures of phenolic compound are studied till now.[8] The carbon's atomic number is 6, i.e. it has 6 electrons and 6 protons. Electrons are around the atom's nucleus in orbitals. The benzene ring is representing one of two mesmeric complexes. The double arrow indicates the two drawn structures and the true structure of the molecule lies in between. Hence, as the six C-C bonds of the ring are identical, with the π-electrons over the entire ring which is more accurate to use structure. The affects of reactivity of aromatic compounds is due to delocalization of the π-electrons is very much favorable and also have tendency to refurbishing aromaticity. Aromatic compounds do not easily undergo any addition reactions and a double bond is replaced by two single bonds, as we see in regular alkenes i.e., linear chains of carbon atoms containing at least one double bond. Aromatic compounds show a partially replaced the reactions, that means the replacement of atoms.[9,10] The word phenolics include a very wide group of chemical compound. They can be classified in many ways. Harborne and Simmonds (1964) classified these compound into groups depends upon the numeral of carbons in the molecule. (Table 1).[9]

Table 1: Classification of phenolic compounds.

Structure	Class
C6-C1	Simple phenolics
C6-C2	Phenolic acids and related compounds
C6-C3	Acetophenones and phenylacetic acids
C6-C3	Cinnamic acids, cinnamyl aldehydes, cinnamyl alcohols
C15	Coumarins, isocoumarins, and chromones
C15	Chalcones, aurones, dihydrochalcones
C15	Flavans
C15	Flavones
C15	Flavanones
C15	Flavanonols
C15	Anthocyanidine
C15	Anthocyanine
C30	Biflavonyls
C6- C1- C6, C6- C2- C6	Benzophenones, xanthones, &$$$;tilbenes
C6, C10, C14	Quinones
C18	Betacyanine

Health benefits of phenolic compounds

Phenolic compounds can be found in various fruits and vegetables, especially grapes, berries, and tomatoes. Phenolic compounds can benefit one's health by reducing the risks of developing metabolic disorders, such as type 2 DM. The biological properties of phenolic compounds are diverse, although the specific mechanisms they exert their disease preventive effects remain unknown. Antioxidants contribute to the removal of these oxidative products. Under normal cellular circumstances, ROS and reactive nitrogen species (RNS) are incredibly reactive molecules; for example, ROS and RNS can disrupt mitochondrial respiration, damaging critical biological macromolecules, including proteins and DNA.[11–13] The anti-inflammatory, anti-aging, antiproliferative, and antioxidant properties of phenolic compounds have been described in several studies. In totaling the upstairs modifications, antioxidant enzymes are crucial for preventing oxidative damage.[14] Reactive oxygen (ROS) and reactive nitrogen (RNS) species are highly reactive oxidized molecules, including superoxide, peroxide, singlet oxygen, hydroxyl radical, nitric oxide (NO), and peroxynitrite (OONO−), that are constantly produced under normal cellular conditions, such as during homeostasis, impaired antioxidant functions can lead to cellular damage, resulting in aging, disease, and cell death.[15]

Bioavailability of phenolic compounds

The primary sources of phenolic compounds are fruits,[16] vegetables, and beverages, such as coffee, tea, wine, and fresh fruit juices. Although Coffee is known for its

stimulating properties attributed mainly to caffeine, it also contains other biologically active compounds, including phenolic compounds, with chlorogenic acids being the most abundant. The critical factor that affects these compounds in green coffee is the roasting time–temperature profile.[17] Polyphenols found in green tea include, but are not limited to, epigallocatechin gallate (EGCG), epigallocatechin, epicatechin gallate, and epicatechin; flavanols such as kaempferol, quercetin, and myricetin are also found in green tea.[18] In addition to exploring the potential protective effects, these compounds provide health benefits against chronic diseases, understanding the modifications during food processing techniques and, therefore, overall bioavailability is essential. The bioavailability of bioactive compounds is the absorptive process of these molecules across the intestine into the circulatory system, after food ingestion. Several polyphenols can be ingested as either purified, isolated substances or in foods. Following the intake of polyphenols ranging from 6.4 to 1000 mg/day, detectable plasma levels ranged from 0.072 to 5 µM.[19] The polyphenol intake measured for an older Japanese population was reported to range from 183 to 4854 mg/day, with average information of 665–1492 mg/day. Coffee and green tea was the most common sources of these compounds.[20] Phenolic acids typically constitute approximately one-third of the total phenolics consumed, whereas flavonoids comprise the remaining two-thirds. Phenolic and polyphenolic products, either alone or in combination with vitamins, such as carotenoids, vitamin E, and vitamin C, can serve as antioxidants to protect various tissues in the human body from oxidative stress. Polyphenols are the most common antioxidants found in fruit and vegetable-based diets. Gallic, ellagic, protocatechuic, and 4-hydroxybenzoic acids are the most common benzoic acids consumed by humans, whereas caffeic, ferulic, sinapic, and p-coumaric acids are the most common cinnamic acids. Plant-based diets are commonly high in polyphenols, providing nutritional advantages and protecting against the emergence of chronic diseases. However, food processing techniques, including blanching and thermal treatments, can alter polyphenol levels or induce conversion into secondary compounds. Enzymatic and nonenzymatic reactions can activate the absorption and metabolism of phenolics, in addition to molecular changes that might occur during food production. Conjugation reactions may also increase or decrease the bioavailability of these molecules.[21]

Role of phenolic compounds in various disease

Current studies have associated that consuming the foods are abundant in PC are beneficial in prevention of non-communicable diseases or lifestyle disorder which includes cardiovascular diseases, certain group of cancer, and diseases associated with aging.[22] The biological effects acquired from PC were trait to antioxidant properties.[23]

They are as follows.

Alzheimer's disease (AD): inhibition of cholinesterase

AD is a progressive, age-related neurodegenerative disease that represents the most predominant form of dementia. The rapidly aging human population has increased the incidence of AD worldwide, and global AD rates are projected to improve immensely, particularly in developing regions. Although the exact pathogenesis of AD has yet to be clarified, it is currently believed to be a multifactorial disease. Postmortem research performed during the mid-1970s showed that choline uptake and acetylcholine levels were diminished in the cerebrums of AD patients, which was associated with severe presynaptic cholinergic deficits.[24] This finding prompted the cholinergic-deficiency hypothesis, which suggests that a disruption in the cholinergic capacity is an underlying factor in AD development, associated with deficits in learning, memory, behavior, and excitatory reactions in various cerebral regions, including the neocortex and the hippocampus. Acetylcholine is rapidly hydrolyzed by acetylcholinesterase (AChE), and acetylcholine levels at the synapse are responsible for the conduction of electrical impulses that transmit from one neuron to the next, which becomes diminished under conditions of acetylcholine deficiency. Butyryl cholinesterase (BChE) is a catalyst firmly identified with AChE and serves as a co-regulator of acetylcholine hydrolysis and cholinergic neurotransmission.[25] During AD progression, some studies have shown expanded activity of BChE in the most affected brain regions. The inhibition of both AChE and BChE increases acetylcholine availability and diminishes amyloid-beta accumulation, significant AD features. BChE expression is primarily restricted to the fringe tissues, with only small quantities of BChE found in the primary cerebral cortex. The potential advantages of the specific inhibition of AChE without inhibiting BChE could result in reduced responses due to the remaining cholinesterase activity in the fringe regions.[26]

Skin cancer

Phenolic compounds that can affect the cell cycle represent promising natural compounds that inhibit malignant growth, such as skin tumors. Curcumin, which is a well-known apoptotic compound, is one possible compound. Studies have shown that p53 is not activated by curcumin, which is significant for treating p53-transformed melanomas that are impervious to regular chemotherapy. Curcumin activates caspase-3 and caspase-8 but not caspase-9, and, through a layer intervened system, apoptosis happens.[27-29] The chemopreventive effects of polyphenols as anthocyanins, ellagitanins, EGCG, oleuropeindihydroxy phenyl, punicalagin, quercetin, resveratrol and the aflavin, were mainly examined in treatment of melanoma as the highly metastatic form of the cutaneous cancer. These polyphenols are mediated by several signaling pathways against skin carcinogenesis and metastasis, implying the importance of polyphenols to open up new horizons in development of anti-skin cancer therapeutic strategies.[30]

Psoriasis

Psoriasis is a hereditary disease characterized by cutaneous irritation, expanded epidermal growth, hyperkeratosis, angiogenesis, and strange keratinization, with a T cell infiltration into the inflamed skin tissue.[31,32] Psoriasis is often characterized by dry or red patches of skin, coated with gleaming scales and red lines, and can affect various regions of the body, and all areas of the skin can be affected. Psoriasis often presents in the fingernails and toenails, on the skin of the trunk, elbows, knees, and scalp. Skin injuries, breaks in the skin, aggravation, scratching, joint pain, increased irritation of the eyes, and small flaky skin spots on the skin, particularly among infants, are additional symptoms. Irritation and angiogenesis correspond with the pathophysiology of psoriasis, promoting uncontrolled keratinocyte outgrowth. To date, psoriasis, alongside natural elements, is solidly distinguished as a solid, unique hereditary background.[33,34] However, existing treatments can aggravate symptoms and induce phototoxicity, excessive sensitivity, organ damage, malignant growth, and systemic immunosuppression, and the identification of natural treatment options represents a vital alternative.[35] Immunosuppressive and growth mitigation effects against psoriasis have been demonstrated by various natural compounds, including polyphenolic compounds.[35] Psoriasis is a stable, recurring skin disease that affects up to 2% of the global population, characterized by well-defined macroscopic skin changes.[36] The development of psoriatic lesions involves two diverse cell types, mononuclear leukocytes, and epidermal keratinocytes. Keratinocytes produce factors that enable T cells and antigen-presenting cells to communicate directly.[37] Dietary activities have been linked to reductions in the clinical course and incidence of psoriasis in evidence-based clinical studies.[38] Dietary alterations can also diminish the incidence of side effects associated with the use of immunosuppressive drugs; from a pharmacoeconomic perspective, a well-balanced diet can lessen the costs of chronic disease care while also lowering the risks of complications.[39] It has been demonstrated that phytomedicine, which is used for psoriasis patients, provides some advantages, including natural sources, a lower risk of adverse effects, and the avoidance of dissatisfaction with conventional therapy. The herbal products' structural diversity and multiple mechanisms of action have enabled the synergistic activity to mitigate psoriasis through the inhibition of keratinocyte-proliferation.[40]

Acne vulgaris

The anaerobic bacterium Propionibacterium acnes play a significant role in the pathogenesis of skin inflammation. Antimicrobial treatments applied to the treatment of skin rashes, rosacea, and other non-resistant infections may also prevent Propionibacterium acnes colonization. A minimal skin inflammatory response following the application of antimicrobial agents, such as erythromycin and antibiotics, has been reported, leading to a lack of satisfaction with treatment. Benzoyl peroxide (BPO) is an exceptionally viable antibacterial agent against Propionibacterium acnes, which has no known targeted treatment option to date. In a combined treatment for skin rashes, including antimicrobials, retinoids represent a fundamental component and may represent an alternative treatment option.[41] Flavonoids identified in Eucalyptus maculata extract or Terminalia arjuna.[42] include alpha-mangostin, the principal compound in mangosteen natural skin products, which demonstrated significant antimicrobial activity against Propionibacterium acnes strains.[43] Honokiol and magnolol (isolated from Magnolia sp.), in addition to gallic, caffeic, chlorogenic, ferulic, myricetin, and cinnamic acids, quercetin, apigenin, luteolin, and thymol, derived from wild watermelon leaves, are other phenolic compounds that have demonstrated antibacterial effects against Propionibacterium acnes.[44]

Antiseptic

PC has effects on human health which was revealed by Bravo in 1998.[46] PC was used phenol as an antiseptic from ancient times. Now a day, it is no longer used due to, its side effects on living tissues that create blister formation especially on high concentrations. As an antiseptic agent, it is effective against the bacterium *Staphylococcus aureus* i.e. 5% (w/v) solution of phenol. It is used as an oral esthetic with the concentration of 1.4% in throat pastille. It is also in sunscreens lotions. It helps to prevent sunburns due to the presence of the aromatic ring which is an effective absorbance of the UV-B radiation (ranging from 280 and 315 nm) from the sun. It was widely used since the 1970's and nowadays due to the formation of skin rashes and acne the usage is reduced.[47,48]

Antioxidant

The oxidative damage and an imbalance to large biomolecules, like lipids, DNA, and proteins may be due to overproduction of oxidants in physical body. This damage includes the pathogenesis of many human diseases i.e. cardiovascular diseases (CVD), certain sorts of cancers and aging. Thus, it could be a crucial role for the prevention and treatment of chronic diseases by antioxidant phytochemicals which are demonstrated to have antioxidant abilities in human studies. Compounds are scavenging radicals that are referred as antioxidants. The important anti-oxidants are vitamin C and vitamin E. A lack of vitamin C in the diet leads to scurvy. The symptoms include rotten gums, purple lesions on the skin, loss of teeth etc. Vitamin E is a mixture of α-, β-, γ, and δtocopherol in that α-tocopherol is the most effective. Vitamin E is lipid-soluble and has the ability to disrupt the chain reaction at the time of lipid peroxidation. They provided many health benefits by antioxidant activity of polyphenols.[47,49]

Protective against cardiovascular diseases

Polyphenols are helpful for preventing and treating CVD by antioxidant activity and also by other bioactivities such as preventing platelet aggregation. Anti-

inflammation and adhesion which includes oxidative stress and other damage because they owe other physiological effects, like blood pressure reduction etc.[50]

Anti-obesity activity

This activity includes quercetin which may be mediated by mitogen-activated protein kinases signaling pathways (MAPK) and the adenosine monophosphate-activated protein kinase (AMPK), respectively in mature adipocytes and pre adipocytes.[51]

Anti-diabetic activity

Due to hyperglycaemia and hyperlipidaemia, diabetes is usually associated by expand the yielding of free radicals or oxidative stress. There is a remarkable decrease in plasma antioxidants in diabetes and its complication. The metabolic homeostasis was better, and the development of T2D and its complications was observed in Cohort studies showed that was retard or prevented by taking of whole grain foods. PCs such as flavonoids and phenolic acids are helpful in promoting health by decreasing the high risk of metabolic syndrome and the associated complications of type 2 diabetes.[52-58]

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