



Selected potential pharmaceutical and medical benefits of phenolic compounds: Recent advances

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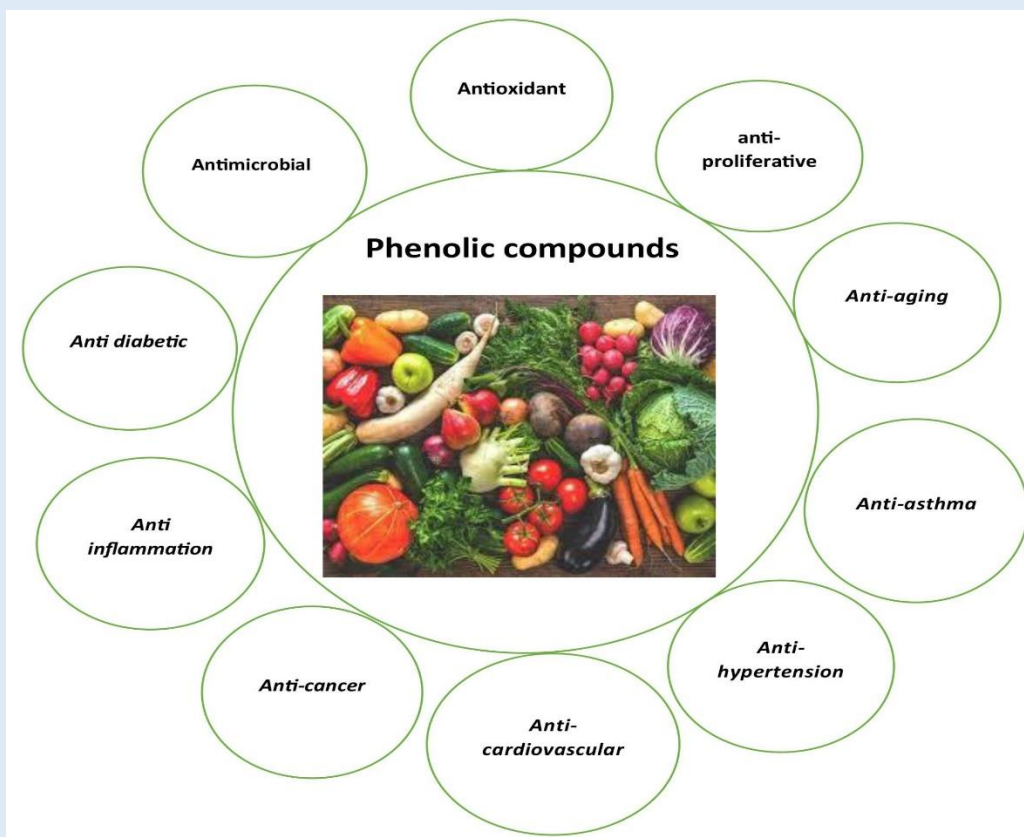
ABSTRACT

Objective: Phenolic compounds are essential for defense reactions, including antioxidant, anti-inflammatory, antidiabetic, anti-proliferative activity, and anti-aging activity. Coming from the class of phytomedicine, they are widespread in the plant kingdom and are commonly taken as substances in the daily diet. They are mainly found in various types of edible plants, especially fruits, vegetables, and tea. Phenolic compounds have been investigated for their effects on human health due to their beneficial effects against oxidative stress activities. The proposed main mechanism of this protective effect against harmful oxidation processes is related to the radical scavenging activity of the phenolic compounds due to reactive oxygen and nitrogen substances.

The review uses up-to-date data via manual screening of the titles and abstracts of retrieved articles using string pharmaceutical and medical benefits of phenolic compounds as keywords to obtain publications from the electronic databases PubMed and Google Scholar using the publish or perish tool. However, priority has been given to the scientific papers, reports, and literature issued within the past 5 years.

Several types of research have been conducted on phenolic compounds due to their potential pharmacological activities. Dietary intake of phenolic compounds is also associated with reducing the risk of cardiovascular disease, mainly caused by oxidative stress and behavioral risk factors such as alcohol abuse, tobacco use, a high-fat diet, and a sedentary lifestyle. They are effective in fighting against various types of diseases.

Conclusion: This review article highlights the currently available information and knowledge on the potential pharmaceutical and health benefits of phenolic compounds.



Keywords: Phenolic compounds, flavanoids, Heart disease, Antioxidant, Cancer, Diabetes mellitus

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INTRODUCTION

Phenolic compounds are considered secondary metabolites and can be divided into flavonoids and non-flavonoids. The flavonoids consist of two aromatic rings linked by an oxygen heterocycle. Depending on the heterocycle exchange and degree of hydrogenation, they can be divided into flavones, anthocyanins, isoflavones, flavanones, and flavonols, which normally occur in nature as glycosides (Fig 1). The other group includes non-flavonoids such as cinnamic acids and benzoic acids, which are two of the most representative compounds of this type and are commonly recognized as phenols,

lignins, stilbenes, and tannins (Fig 2). Recently, there has been a significant increase in interest in the use of phenolic compounds due to their natural effects and promising therapeutic applications. The phenolic compounds found in many foods have significant bioavailability for humans and are therefore considered critical functional products [1] These include phenolic acids, flavonoids, coumarins, styrene-butadiene rubber, tannins, and lignans [2]. Phenolic compounds have many positive contributions to health and have been investigated in many studies for this purpose [3,4].

Interest in phenolic compounds has increased due to their antioxidant properties. Their free radical scavenging properties help to prevent chronic diseases associated with oxidative stress, such as cardiovascular, cancer and neurodegenerative diseases [5]. Phenolic compounds from various food sources have been extensively studied

for their medicinal, pharmaceutical, and health-promoting effects on the human body in many types of research [6-25]. This article highlights selected potential health benefits of phenolic compounds from various sources

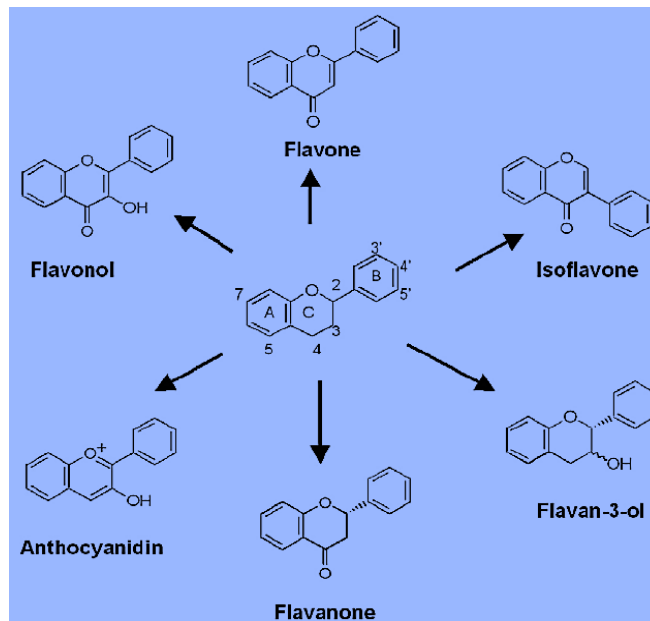


Figure 1. Basic common structure of the principal groups of flavonoids

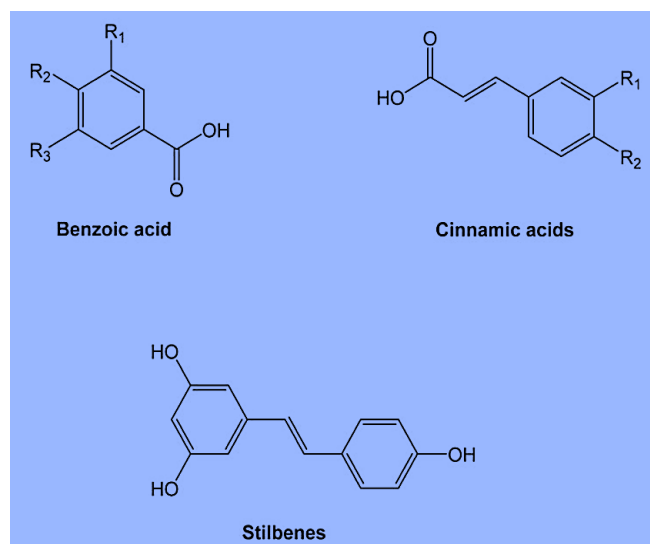


Figure 2. Basic common structure of the principal nonflavonoids compounds

General 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 diabetes mellitus [26]. They are also investigated for their effects on anti-aging, and antioxidant, anti-inflammatory, antiproliferative properties in several studies [27, 28]. The biological properties of phenolic compounds are diverse, although the specific mechanisms they exert their disease-preventive effects remain unknown. Many studies reported the presence of phenolic compounds in various food sources [Table 1] and their health benefits in the human body [Table 2]. According to many studies, phenolic compounds have shown antimicrobial activities [29]. Phenolic compound consumption has been linked to gut microbiota [30]. However, in vivo, and in vitro studies

have shown a possible prebiotic effect of polyphenolic compounds [31]. Recently, the consumption of a diet high in polyphenols (~3 g/day) was investigated and revealed in the human body to significantly increase microbial diversity, which was associated with improved metabolic health [32]. In addition, much attention has been paid to phenolic compounds in vivo [33] and in vitro [34] studies. Phenolic compounds could prevent the activity of gastric enzymes like amylases and lipases, decreasing the absorption of fat and dietary carbohydrates in the gut and causing a reduction in lipid and glucose metabolism. This activity may explain the effect of phenolic compounds on the postprandial stage [35, 36]. The composition of lipoprotein can be also influenced by phenolic compounds as they regulate important enzymes involved in the dynamic exchange of lipids.

Table 1: Selected phenolic compounds and their food sources

S.no	Name of phenolic compound	Source of food	Reference
1	Condensed tannins, epicatechin polymers, Tannins, catechin polymers	Grapes, pear, Lentils, peaches, mangosteens, plums, and apple juice	[37]
2	Flavonols, Isorhamnetin, Kaempferol, Quercetin, Isorhamnetin, Myricetin	Apples, onions <i>Allium cepa</i> , cranberries, plums, strawberries, kale, broccoli, tomatoes, olive, grape juice, and green tea	[38]
3	Lignan, secoisolariciresinol, matairesinol, medioresinol, pinoresinol, lariciresinol	Buckwheat, flaxseed, sesame seed, and wheat	[39,40]
4	Hydrolyzable ellagitannins, casuarictin, tannins, punicalagin.	Raspberries, strawberries, walnuts, blackberries, and fruit husk	[41]
5	Resveratrol, stilbenes	Peanuts, red cabbage, berries, grapes, spinach, berries, pine nuts, and plums	[42]
6	Aesculetin, coumarins, umbelliferone	Citrus fruits, celery, carrots, and parsley	[43]
7	Luteolin, apigenin, flavones	Green olive, parsley, celery, artichoke, onion, sweet peppers, garlic, spinach, and citrus fruits	[44]
8	Umbelliferone, coumarins, aesculetin	Parsnips, celery, carrots, citrus fruits, and parsley	[45]
9	Genistin, isoflavones, glycitein, daidzein	Soybeans, soy products, and chickpeas	[46]
10	[+] -Catechin, flavan-3-ols, [-] - fpicatechin	Sour cherries, Tea, grapes, apples and blackberries, nuts, plums, and chocolate	[47]

Table 2: Protective activities of phenolic compounds against selected diseases

S.no	Disease	Phenolic compound used	Mode of activity	Reference
1	Alzheimer's disease	Hesperidin, kaempferol, apigenin, and benzoic acid.	Antityrosinase, anti-amylase, and anti-glucosidase activity	[48]
2	Ischemic stroke	3, 4-Dihydroxybenzaldehyde	Reducing the production of inflammatory mediators and cytokines	[49]
3	Human cancer	Chalcones, benzofurans, alkaloids	Act as anti-Human cancer cell line	[50]
4	Aspergillosis	Carvacrol, thymol and Eugenol	inhibit mycelia growth and disrupt the fluidity of cell membrane	[51]
5	Zygomycosis	Thymol	interact with ergosterol and disrupt fluidity	[52]
6	Candidiasis	Carvacrol, thymol and curcumin	Inhibit Biofilm formation and morphogenetic switch	[53]
7	Cryptococcosis	Benzoic acids, Thymol and 2,5-dihydroxy benzaldehydes	Synergistic enhancement of fungicide	[54]
8	cardiovascular diseases	Caffeic acid	in vitro and in vivo Inhibition of LDL oxidation	[55]
9	Diabetes	Quercetin, kaempferol, naringenin, apigenin	showed significant hypoglycemic	[56]

This phenomenon occurs between the enzymes related to the metabolic processes that take place in the liver and these different lipoproteins in the plasma [57]. On the other hand, phenolic compounds such as flavan-3-ols and anthocyanins may improve insulin sensitivity observed after eating meals containing them [58-60]. This effect may be due to the reduction in cellular stress, which could translate into cell maintenance, and increased peroxisome proliferator-activated receptor gamma (PPAR), resulting in improved insulin sensitivity of adipose tissue, modulation of adipogenesis, and possibly the high glucose uptake in both adipose tissue and muscle [61]. Phenolic compounds could also protect the skin from damage caused by vital processes such as replication, transcription, and translation, leading to increased pathological processes, necrobiosis, mutation, and aging [62].

PROTECTION ACTIVITIES OF PHENOLIC COMPOUNDS

Antimicrobial activities: Phenolic compounds are being

studied for their antifungal effects and have shown positive major antifungal activities [63]. The antimicrobial activities of many phenolic compounds, including quercetin, gallic acid, coumarin, caffeic acid, catechin, and tannin have been studied [64]. The study showed that these phenolic compounds exhibited significant antibacterial activities against the microorganisms tested. It has been observed that gram-negative bacteria such as *Pseudomonas* and *Escherichia coli* generally have higher antimicrobial susceptibility than gram-positive bacteria such as *Bacillus*. The results showed that gallic acid had a significant effect against *Bacillus subtilis* but showed a more potent effect against *Pseudomonas aeruginosa* and *Escherichia coli*. In another study, the inhibitory activities of 25 natural phenolic compounds were tested against three strains of *Streptococcus pyogenes* [65]. The results showed that 5-hydroxy-1,1,2-naphthoquinone and 4-naphthoquinone

inhibit *Streptococcus pyogenes* and could be used as good candidates to control this bacterium. Several natural phenolic acids have been studied for their antifungal activities and they are approved and considered as biofungicides in many research areas [66-59]. Inhibition of fungal pathogens of many phenolic acids such as p-coumaric acid, caffeic acid, vanillic acid, gallic acid, ferulic acid, and syringic acid has been demonstrated against *Fusarium oxysporum*, *Fusarium verticillioides*, *Penicillium brevicompactum*, *P. expansum*, *Aspergillus flavus*, and *Aspergillus fumigatus* [70]. Caffeic and gallic acids individually had no effect on *Candida tropicalis* but had a synergistic effect when combined with fluconazole (Samarghandian et al., 2017). Several different phenolic chemicals are produced by certain plant species. Catechin is a substance found in *Camellia sinensis* and *Camellia assamica*. Green tea's main ingredients are water and phenolic compounds (phenolic acid, flavandiol, flavanols, and flavonoids), and more than 75% of the polyphenols in tea leaves are catechins [71]. Active catechin $C_{60}(OH)_{44}$ is frequently utilized as a regulator in fullerene investigations, and its hydroxylated derivatives have antibacterial properties. Alvarez-Suarez et al. [72] investigated the presence of carotenoids, flavonoids, amino and ascorbic acids, proteins, and total phenolic compounds and explored their antimicrobial properties.

Anti-diabetic: Untreated diabetes is considered a life-threatening disease worldwide [39, 40]. According to the WHO [73], diabetes is characterized by a state of metabolic disorders that leads to an increase in blood

sugar levels (hyperglycemia) above normal limits. It has been reported that phenolic compound intake can play a fundamental role in the management of diabetes as it can reduce protein glycation, blood sugar levels, and oxidative stress. They can also inhibit the activity of enzymes related to carbohydrate metabolism, improve insulin resistance, and increase insulin secretion [74]. It has been described as a civilization disease of the 21st century. Mainly non-enzymatic protein glycation and oxidative degradation of glycated proteins have been implicated in oxidative stress causing diabetes. Many factors, such as lipid peroxidation, enzymes, and cell damage, can subsequently lead to the progression and development of hyperglycemia and insulin resistance [75]. The main components of drugs used to treat diabetes, such as voglibose, miglitol, and acarbose, work by inhibiting amylase and glucosidase. Therefore, scientists are interested in finding natural inhibitors like phenolic compounds to treat diabetes [76]. Numerous studies have reported the potential of phenolic compounds to protect against diabetes mellitus. Their potential phenolic compounds have been demonstrated by: 1) enhancing insulin action; 2) regulating carbohydrate metabolism to improve glucose uptake; 3) regulating critical signaling pathways that protect cell homeostasis of pancreatic cells; and 4) improving glucose uptake [77-80]. Phenolic compounds comprise a large group of naturally occurring molecules known for their hypoglycemic properties. For example, phenolic acids and flavonoids have been suggested to inhibit amylase and glucosidase and help treat type 2 diabetes [81]. Most phenolic acids have been reported to show significant antidiabetic activities in vivo and clinically [82]. Additionally, one of the best-reported ways to prevent diabetes is to eat foods rich in polyphenols [83-86]. Phenolic compounds from various sources have been used extensively in treating diabetes [87-89]. Insulin sensitivity has been observed after taking phenolic

compounds, particularly flavan-3-ols and anthocyanins [90]. According to in vitro studies, this effect could also be related to many factors, including [1] the reduction of cellular stress, which could translate into cell maintenance and/or [2] the improved expression of the peroxisome proliferator-activated receptor gamma [PPAR] and activated glucose transporter protein 4 [GLUT-4]. As a result, the glucose transporter protein 4 [GLUT-4] could be activated, improving adipose insulin sensitivity, modulating adipogenesis, and increasing glucose uptake in muscle and adipose tissue [91]. Naringenin and naringin flavanones have been reported to produce antidiabetic effects by enhancing the expression of glucose transporters and insulin receptors in type 2 diabetic rats, thereby improving insulin resistance [92,93]. A similar observation has been reported with the procyanidin, cinnamannin A2, which improves glucose tolerance and prevents hyperglycemia [94]. In addition, another flavanone, hesperidin, has been reported to reduce oxidative DNA damage and lipid peroxidation and improve glycemic control associated with hyperglycemia in patients with type II diabetes [95]. Ambriz-Prez et al. [96] found that phenolic compounds extracted from malaca pulp at concentrations of 100 and 200 mg/kg significantly lowered blood glucose levels in diabetic-induced rats. This finding may indicate that the phenolic extract of the fleshy fruit of Malaca can be used successfully as an anti-type 2 diabetes mellitus treatment without negative side effects. Previously, Bhandari et al. [97] investigated the antidiabetic efficacy of *Bergenia ciliata*. The active chemicals (-)-3-O-galloylprocatechin and (-)-3-O-galloylcatechol, found in the ethyl acetate soluble *Bergenia ciliata* extract, were found to be responsible for the substantial inhibition of porcine and pancreatic amylase of the intestinal maltase from rats are dose-dependent.

The half-maximal inhibitory concentration (IC50) values for (-)-3-O-galloylcatechol were 334 and 739 M,

respectively, for rat intestinal maltase and porcine pancreatic amylase, and those for (-)-3-O-galloylcatechol were 150 and 401 M, respectively. Delaying glucose uptake by inhibiting α -glucosidase activity is a possible treatment option for the prevention of type 2 diabetes mellitus. They also claimed that natural health substances, including non-flavonoid polyphenols such as curcumin, resveratrol, lignans and tannins, and flavonoids such as epigallocatechin gallate, anthocyanins, quercetin, rutin, kaempferol, and naringin, and vegetables, plant fruits, and other products such as green tea, garlic, rowanberry, blackcurrant, strawberry, blueberry, sesame oil, olive oil, carrot, and cornel may be a safer alternative to primary pharmacological therapy [97] (Bhandari et al., 2008). Blahova et al. [98] reported that flavonoids should be considered essential components of the human diet as they contribute to treating type 2 diabetes mellitus (T2DM) by delaying the deterioration of pancreatic beta cell function caused by oxidative stress. They are recommended as dietary supplements for the prevention and relief of T2DM-related complications.

Anti-inflammation: Inflammation is recognized as a biological response caused by a disruption in tissue homeostasis and occurs in response to the presence of physical, biological, chemical, or drugs in the body [99]. Some of these agents may include toxic compounds, immune system reactions, pathogens, and trauma [100]. Chronic inflammation and acute inflammation occur according to the intensity and nature of the stimulus response involved in removing the stimulus or the injured tissue [101]. Inflammation is often treated with synthetic drugs, which are often associated with dangerous side effects resulting in difficulty in treating the condition, including long-term use, iatrogenic reactions, and drug-related toxicity [102,103]. As a result, this can cause stomach ulcers, gastrointestinal bleeding, osteoporosis,

liver failure, rashes, and cataracts, among other side effects [104]. Therefore, in recent decades, more effective and safer anti-inflammatory agents from natural traditional medicine, such as phenolic compounds, must be used for their effectiveness in treating several human diseases [105]. Additionally, phenolic compounds have anti-inflammatory because they regulate cell activity in inflammatory cells and modulate the activities of enzymes involved in the metabolism of arachidonic acid (lipoxygenase, phospholipase, and cyclooxygenase), arginine metabolism, and the secretion of pro-inflammatory molecules [106].

Phenolic compounds have been studied for their anti-inflammatory activities [107-110]. As a result of their success in disrupting the ROS-dependent inflammation cycle, they approved anti-tumor necrosis factors and also regulated the expression of transcription factors such as nuclear factor kappa light chain enhancer of activated B cells [111]. When the inflammatory process occurs, reactive oxygen species [ROS] and reactive nitrogen species [RNS] are produced, resulting in an increase in pro-inflammatory activity [112]. The anti-inflammatory effect of phenolic compounds results from a ROS-dependent disruption of the inflammatory cycle [113]. Phenolic compounds also act against pro-inflammatory mediators such as tumor necrosis factor and can also regulate the expression of transcription factors such as nuclear factor kappa light chain enhancer of activated B cells [114]. Recently, Bouhlali et al. [115] studied the anti-inflammatory activity of Jihl phenolic extracts obtained from four Moroccan date (*Phoenix dactylifera* L.) seed varieties at a concentration of 30 mg/kg in Wistar strain rats. They found that they have anti-inflammatory properties via reducing the capacity of lysosomal membranes to stabilize C-reactive protein and fibrinogen P, as well as inhibition-mediated protein denaturation and nitric oxide free radical scavenging. These findings

might be attributed to the presence of phenolic substances such as rutin, quercetin, p-coumaric acid, and caffeic acid in various date seed types, and notably Jihl seeds, which had the highest anti-inflammatory action among the date seed varieties studied.

Anti-cancer: Recent research has been devoted to studying the anticancer properties of phenolic compounds [116,117]. The anticancer properties of phenolic compounds are based on their action on intrinsic and extrinsic factors, reduction by interfering with the metabolism of procarcinogens by regulating the expression of cytochrome P450 enzymes, increase in elimination by increasing the expression of conjugating phase II enzymes and production of toxic substances. Quinones are the substrate of this enzyme in the body [118]. Therefore, their absorption can stimulate the activity of detoxification cations, resulting in protection against toxic xenobiotics and stimulation of apoptosis of tumor cells and inhibition of angiogenesis, which reduces the growth of a tumor. Some people believe that phenolic compounds inhibit cancer mainly in the early stages because most of these compounds act as free radical scavengers [119]. According to the studies [120], in vivo investigations have shown that phenolic compounds can delay and/or inhibit the development of various forms of cancer since they can act by regulating gene expression and cell signal transduction, which can be either down- or up-regulated of genes that control tumor development. In addition, the production of higher reactive oxygen species [ROS] has been demonstrated in many cancers and implicated in the activation of increased cellular survival, protumorigenic signalling, proliferation, and thus the induction of DNA damage [121]. The chemopreventive effects of polyphenols such as ellagitannins, anthocyanins, oleuropeindihydroxy phenyl, quercetin, punicalagin, theaflavin, and resveratrol were mainly examined in

treatment of melanoma as the highly metastatic form of cutaneous cancer [122]. The actions of polyphenols against cancer and metastasis are mediated by several signaling pathways, suggesting that polyphenols could open new therapeutic horizons for the fight against cancer [123].

Phenolics compounds have shown remarkable health-promoting effects, including anti-inflammatory and antioxidant properties, as well as anti-cancer properties, based on epidemiological evidence [124]. The anticarcinogenic properties of phenolics have been studied in numerous cell lines, including ferulic, feruloyl-l-arabinose, and coumaric [125]. Apoptosis, cell proliferation, invasion, and apoptosis are all inhibited by ferulic acid in MIA PaCa-2 cells (human pancreatic cells) [126]. In a study examining the synergistic effects of ferulic acid and tocotrienol on various cancer cells, researchers discovered that, when combined, these compounds inhibit the proliferation of prostate cancer cells, breast cancer cells, and pancreatic cancer cells more effectively than when they are used separately [127]. According to Choi and Park [128], breast cancer cells are inhibited in their production of RAD51 (eukaryotic gene) after homologous recombination activity is suppressed by ferulic acid during DNA repair. The phenolic compound such as p-coumaric acid also inhibited the growth of Caco-2 colon cancer cells, protecting against its development [129]. Earlier, feruloyl-l-arabinose inhibited cell penetration, ROS, and motility generation in lung cancer cells [130]. Furthermore, anticarcinogenic properties have been reported for flavonoids like troxerutin, apigenin, kaempferol, and myricetin [131].

Anti-cardiovascular: Globally, cardiovascular diseases are recognized as the number one cause of death and are projected to remain [132]. In addition to cardiovascular disease and hypertension, there are several other

diseases that affect the heart, such as cerebrovascular disease, coronary artery disease (heart attacks), rheumatic heart disease, peripheral artery disease, congenital heart disease, and heart failure [133]. There are major causes of cardiovascular disease, such as physical inactivity, tobacco, and an unhealthy diet [134]. Dietary intake of phenolic compounds is related to reducing the risk of cardiovascular [135]. Cardiovascular diseases are mostly caused by oxidative stress and behavioral risk factors like alcohol abuse, tobacco use, high-fat diets, and sedentary lifestyles [136]. Phenolic compounds also have been studied for their effects on human health due to their beneficial effects against oxidative stress activities [137]. The proposed main mechanism of this protective effect against harmful oxidation processes is related to the free radical scavenging activity of the phenolic compounds because of reactive oxygen and nitrogen substances [138]. Although several systematic reviews indicated that dietary flavonoid intake reduces cardiovascular disease [139], some data did not suggest that flavonoid-rich fruits can affect systolic and diastolic blood pressure [140]. In addition, one meta-analysis that examined 45,732 cases of hypertension from 20 studies demonstrated that flavonoid intake showed no significant association with decreased risk of hypertension, while dietary anthocyanin intake was associated with an 8% reduction in hypertension risk [141].

Anti-hypertension: High blood pressure (Hypertension) is a serious condition and can increase the risk of heart, brain, kidney, and other diseases. It is a leading cause of premature death worldwide, affecting more than 1 in 4 men and 1 in 5 women in over a billion people [142]. Hypertension (HTN) is one of the most dangerous cardiovascular diseases causing nearly 8.5 million deaths worldwide [143]. HTN is a complex and multifactorial disease, and a combination of genetic susceptibility and

environmental factors play an important role in its development. However, the underlying regulatory mechanisms are still elusive [143]. Polyphenols have been seen as beneficial in treating HTN [144]. Increasing evidence has demonstrated the beneficial role of polyphenols in the treatment of hypertension [145]. Godos et al. [146] recently conducted a comprehensive review and meta-analysis of observational research on dietary polyphenol intake and hypertension risk, comprising 15 cross-sectional studies and 7 prospective cohorts. They investigated a meta-analysis of five prospective cohorts, totalling 200,256 people and 45,732 hypertension cases. The quantitative analysis revealed that total flavonoids were not associated with the risk of hypertension, however, anthocyanin consumption was consistently associated with a decrease in hypertension risk among specific subgroups. In other observational studies, individuals who had a diet consisting of more phenolic acids such as and phytoestrogens (including isoflavones) [147,148] and hydroxycinnamic acids [149,150] performed better and were less likely to be hypertensive. Considering polyphenol-rich foods, a comprehensive review of data from seven meta-reviews found that increased consumption of plant-based foods such as fruit, whole grains, nuts, and legumes/pulses was related to a lower risk of hypertension [151-155], even though several of the included meta-analyses were of low quality, compromising the overall strength of the evidence. Vegetable consumption and the risk of hypertension studies showed null results [156,157]. Concerning polyphenol rich plant derived drinks, we conducted the most comprehensive meta-analysis on long-term coffee intake and hypertension risk, involving seven cohorts, 205,349 participants, and 44,120 cases of hypertension, revealing a linear dose-response association [158].

Anti-asthma: Asthma is recognized as a chronic disease characterized by airflow limitation, airway inflammation,

hyperreactivity, and airway remodeling [159]. Asthma is believed to be caused by the interaction between genetic and environmental factors. Over the past two decades, allergic illnesses like asthma, have become more common [160]. Although the exact reasons for this increase are still unknown, dietary changes are believed to be one of the important factors [161]. Flavonoids, the polyphenolic secondary plant metabolites ubiquitous in vegetables, fruits, and beverages, possess antioxidant and antiallergic properties, as well as immunomodulating activities [159]. Flavonoids are powerful antiallergic nutrients and antioxidants that inhibit the release of chemical mediators [162]. Several studies on flavonoids in asthmatic animal models have shown their beneficial effects [163-165]. The results of many epidemiological studies have suggested that increasing flavonoid intake is beneficial for people with asthma [166-169]. Furthermore, clinical studies have demonstrated the alleviating effects of flavonoids on asthma-related symptoms [170] (Yao et al., 2022).

Anti-aging: Aging is recognized as the accumulation of various harmful changes in cells and tissues, increasing the risk of mortality and disease [171]. The free radical/oxidative stress theory is one of the most globally recognized concepts for explaining the mechanisms of aging [172]. Some oxidative damage occurs even under normal conditions; however, as the efficiency of antioxidative and repair systems declines with age, the rate of this damage increases [173]. The antioxidant capacity of plasma is associated with antioxidant food consumption [174]. Consuming an antioxidant-rich diet is believed to help prevent the negative effects of aging and behavior [175]. It was suggested that the consumption of polyphenolics present in fruits and vegetables could be effective anti-aging agents [176]. Brightly colored fruits, such as concord grapes, berry fruits, and grape seeds, are

exceptionally high in anthocyanins, a subset of flavonoids [177].

Fruit pigments called anthocyanins have been proven to have powerful antiaging properties [178]. Vegetable and fruit extracts with high quantities of flavonoids, such as strawberries, spinach, and blueberries, have high total antioxidant activity. It was reported that dietary supplementation with spinach or strawberry extracts in a control diet was likewise helpful in restoring age-related deficiencies in rats [179]. According to a new study, tea catechins have potent anti-aging properties, and drinking green tea rich in these catechins may help delay the onset of aging [180,181]. Polyphenols can help reduce the effects of aging on the brain [182]. Recent reports have shown that dietary polyphenols can improve cognitive function and protect against neurodegenerative diseases such as Alzheimer's and Parkinson's. Polyphenols are a group of plant-derived functional food ingredients with different molecular structures and various biological activities, including antioxidant, anti-inflammatory, and anticancer properties [183]. The Functional Food Center has contributed to an enhanced definition of functional foods. These foods contain biologically active compounds and provide specific and clinically validated health benefits [184]. The blood–brain barrier (BBB) permeability of these compounds allows them to directly interact with brain cells and exert their beneficial effects. The ability of dietary polyphenols to cross the BBB, which tightly limits the entry of metabolites, nutrients, and

medications into the brain, is critical for their relevance in protecting the aging brain [126].

CONCLUSION

In summary, phenolic compounds possess remarkable potential functional properties due to their diverse inhibitory activities. This article highlights recent potential protective activities of phenolic compounds, including antimicrobial, anti-diabetic, anti-inflammation, anti-cancer, anti-cardiovascular, anti-hypertension, anti-asthma, and anti-aging.

List of Abbreviations: BBB: blood–brain barrier, GLUT-4: glucose transporter protein 4, HTN: hypertension, PPAR: peroxisome proliferator, activated receptor gamma, ROS: reactive oxygen species, RNS: reactive nitrogen species, T2DM: type 2 diabetes mellitus.

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Conflict of Interest: The authors declare that there is no conflict of interest related to this article.

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