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Review Article

Bioactive Properties and Mechanisms of Effect of Phenolic Compounds

Merve GÜNDÜZ [1], **Ahmet BEKTEŞ** [2*], **Şeniz KARABIYIKLI ÇİÇEK** [3], **Vildan KİLİNÇ** [4]

[1,2] Tokat Gaziosmanpasa University Graduate Education Institute, Department of Food Engineering, Tokat, Turkey
[3] Tokat Gaziosmanpasa University Faculty of Engineering and Architecture, Department of Food Engineering, Tokat, Turkey
[4] Tokat Gaziosmanpasa University Graduate Education Institute, Department of Plant Protection, Tokat, Turkey

*Corresponding author e-mail: ahmetbektes@windowslive.com

A B S T R A C T

The desire of people to live a healthy and long life has encouraged an increase in interest in natural and balanced nutrition. The production of natural food additives from plant, animal and fungal sources is gaining importance day by day to produce food with natural ingredients. Phenolic compounds commonly found in plants are organic compounds that contributes to improve the textural and sensory properties of foods, as well as enriching their nutritional values, and takes an active role in ensuring food safety due to its antimicrobial, antioxidant and antifungal effects. Studies conducted also show that phenolic compounds can be used in the treatment of infection, obesity, diabetes, cardiovascular health problems and aging. In this review study, the mechanisms of antimicrobial, antioxidant, anti-fungal, anti-biofilm, anti-oxidative stress, anti-inflammatory, anti-obesity, anti-diabetic, anti-aging and cardiovascular effects of phenolic compounds were investigated.

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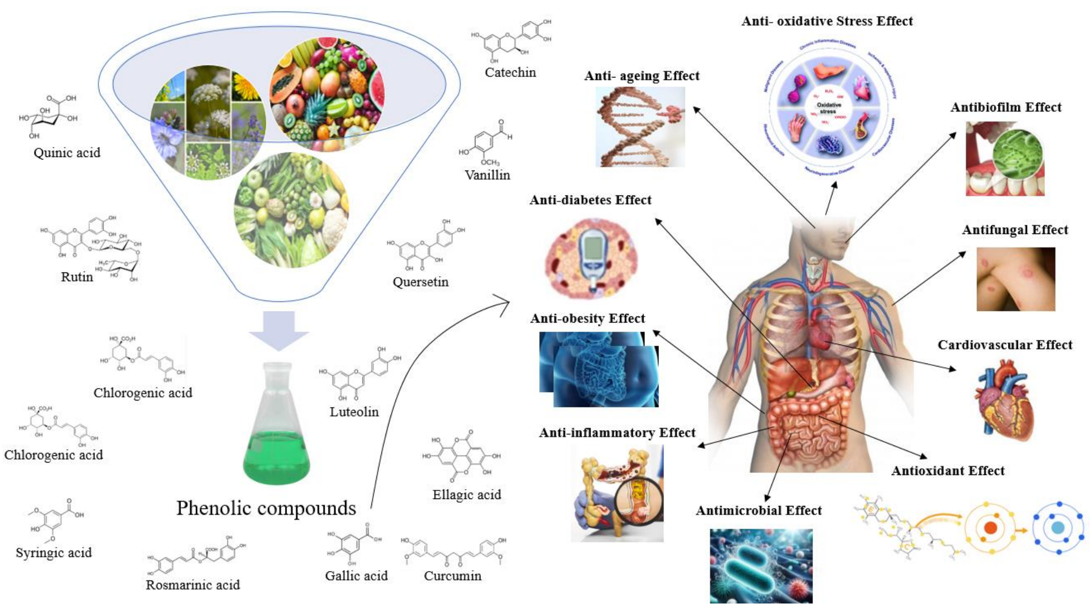

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INTRODUCTION

Phenolic compounds or polyphenols found in various organs of plants (vegetables, fruits, nuts, cereals, legumes, etc.) and described as secondary metabolites are bioactive compounds that play an important role in various physiological phenomena. These bioactive compounds play a role in the formation of organoleptic properties in plants, such as pigmentation, bitterness or astringency. In addition, they act as protective substances in plant defense against UV light, parasites and insects (Alara et al.,2021; Albuquerque et al., 2021).

Phenolic compounds contain a benzene ring (C_6H_6) with one or more hydroxyl groups, also called phenol. As a result of studies to date, phenolic compounds with more than 8000 different molecular structures have been identified (Artık et al., 2016; Cosme et al., 2020; Zhang et al., 2022). Phenolic compounds can be found in free form or in water-soluble or insoluble forms bound with carbohydrates, proteins, organic acids or other biomolecules (Alara et al., 2021; de Araújo et al., 2021). Phenolic compounds are generally classified according to the number of phenolic rings, the substituents attached to the rings and the structural elements that connect these rings. The main classes of polyphenols or phenolic compounds are phenolic acids, flavonoids, chalcones, phenolic alcohols, stilbenes, lignans, coumarins and tannins (Maniglia et al., 2021). However, the main phenolic compounds found in foods are mostly examined in two groups as phenolic acids (hydroxycinnamic acids, hydroxy benzoic acids, hydroxycinnamic acid derivatives) and flavanoids (anthocyanidins, catechins, flavonols, flavones, flavanones, procyanidins, loyco-anthocyanidins and dihydro-chalcones) (Artık et al., 2016; Arfaoui, 2021).

After the discovery of the biological activities of phenolic compounds for various diseases, interest in these compounds has increased day by day. A large number of studies have been carried out in order to improve human health, prevent or treat diseases. When the studies were examined, it was determined that phenolics are agents with beneficial properties in terms of health such as antioxidant, anti-inflammatory, antimicrobial, anti-allergenic, antiviral, anticarcinogenic (Grgić et al., 2020; Zhang et al., 2022), anti-diabetic, anti-biofilm, anti-fungal (Onat et al., 2021) activities, and in preventing diseases such as oxidative stress, obesity, osteoporosis and cardiovascular diseases (de Araújo et al., 2021).

Antimicrobial, antioxidant, antifungal, antibiofilm, anti-oxidative stress, anti-inflammatory, anti-obesity, anti-diabetes, anti-aging and cardiovascular mechanisms of effect were investigated in relation to the bioactivity of phenolic compounds. The explanation of the bioactivity and mechanisms of action of phenolic compounds is of great importance for food scientists and pharmacologists. Food scientists can use them as natural food additives due to the antimicrobial, antibiofilm, antioxidant and antifungal effects of phenolic compounds and the knowledge of their mechanisms of action. Pharmacologists can integrate phenolic compounds into existing treatment methods due to the knowledge of the pathway in which phenolic compounds are effective in the treatment of many diseases, or they can include phenolic compounds in new methods to be developed.

Mechanism of Antimicrobial Effect

Artificial food additives in the food industry have started to be replaced by natural food additives as a result of developing technology. The use of phenolic compounds obtained from plants as natural food additives is increasing day by day due to their antimicrobial effects. It has been confirmed that phenolic compounds have inhibitory effects on many foodborne pathogenic (*Escherichia coli*, *Salmonella* Typhimurium, *Pseudomonas aeruginosa*, *Bacillus cereus*, *Staphylococcus aureus* and *Listeria monocytogenes* etc.) and spoilage causing microorganisms. However, the mechanism of antimicrobial effect of phenolic compounds could not be clearly declared (Martinez-Gonzalez et al., 2017; Pernin et al., 2019).

There are many different theories about the mechanisms of antimicrobial effect of phenolic compounds. The first one of these theories is the hydroxyl groups (OH-) in the structure of phenolic compounds interact with the cell membrane of bacteria, disrupting the membrane structure of the cells and causing cellular components to leak out of the cell. Another theory is; OH- groups in the structure of phenolic compounds cause delocalisation of electrons acting as proton exchangers and decrease the tendency of bacterial cells on the cytoplasmic membrane, causing cell death due to collapse of the proton motive force and decrease in the ATP pool. It is also known that OH- groups can change the enzyme metabolism by easily binding to the active part of enzymes by changing the cell metabolism of microorganisms. While; low concentrations of phenolic compounds affect enzymes responsible for energy production, high concentrations show antimicrobial effect by increasing the denaturation of proteins. As a result, it is possible to explain the mechanisms of antimicrobial effect of phenolic compounds in the form of damage to the cytoplasmic membrane, collapse of protein movement force, disruption of electron flow and coagulation of cell components caused by decreased active transport, leakage of macromolecules such as ribose and Na glutamate from the cell structure, changes in cell membrane permeability and denaturation of protein structure, changes in protein and nucleic acid synthesis mechanisms and changes in enzyme mechanism (Öncül and Karabıyıklı, 2016; Yücel-Şengün and Öztürk, 2018).

The mechanism of fungal inactivation by the combination of phenolic acids and 405 nm irradiation was associated with the formation of H_2O_2 and hydroxyl radicals following 405 nm irradiation of phenolic acid solutions. It was understood that irradiation of phenolic acids caused a significant increase in the level of intracellular reactive oxygen derivatives and it increased cell inactivation. The increase in the level of intracellular reactive oxygen derivatives could not be associated with changes in membrane permeability and ATP content was significantly reduced. These results show that the first stage in the photofungicidal mechanism is the system of oxidative damage to mitochondria or the cellular catabolism system associated with ATP synthesis because of the photoreaction of phenolic acids absorbed by the fungus (Shirai et al., 2022).

The mechanisms of effect of phenolic acids, such as the decrease of extracellular pH in the presence of phenolic acids directly inhibiting growth against *Listeria monocytogenes*, the inhibitory effect of the undissociated acid form, and the inhibitory effect of the dissociated acid form, were all studied. Firstly, chlorogenic acid and gallic acid have a low antimicrobial activity on bacterial development, mainly by inhibiting the growth of *L. monocytogenes* with their ability to lower extracellular pH. Second, caffeic acid, p-hydroxybenzoic acid, protocatechuic acid and vanillic acid exhibit antimicrobial behaviour mainly through the ability of their undissociated forms to inhibit the growth of *Listeria monocytogenes*. Third, p-coumaric acid and ferulic acid similarly exhibit antimicrobial behaviour through their undissociated forms, but their dissociated forms also show significant antimicrobial activity (Pernin et al., 2019).

Valine and chlorogenic acid can cause bacterial death by destroying the surface membrane and internal structure of cells (Lou et al., 2011; Li et al., 2014; Jiang et al., 2020). Quercatinin causes cell death by cell membrane disruption (membrane hardening), DNA gyrase inhibition, Type 3 secretion inactivation, dehydratase inhibition and protein kinase inhibition mechanisms (Plaper et al., 2003; Zhang et al., 2008; Shakya et al., 2011; Wu et al., 2013; Tsou et al., 2016). Apigenin causes dehydratase inhibition and protein kinase inhibition (Zhang et al., 2008; Shakya et al., 2011).

Mechanism of Antioxidant Effect

Phenolic compounds found in plants are known to be powerful antioxidants that prevent oxidative damage caused by biomolecules. The mechanism of antioxidant effect is mainly based on the scavenging of free radicals, inhibition of lipid peroxidation and activation of the endogenous antioxidant system. The antioxidant potential of phenolic compounds is related to their structure and is affected by hydroxyl groups and glycolisation factor. Since hydroxyl groups are a source of hydrogen and electrons, their number and position are related to the antioxidant effect of phenolic compounds. The presence of substituents in the aromatic ring affects the radical trapping activity due to the stabilisation of the molecule. Glycolysis of compounds is also known to affect antioxidant activity as it interferes with the structure, methylation, and electron displacement of the molecule. It has also been observed that methylation of compounds reduces antioxidant ability (Ferraira et al., 2017; Kumar and Goel, 2019; Vuolo et al., 2019).

Studies have shown that phenolic antioxidants have significant free radical scavenging activity due to their capacity to donate hydrogen atoms or electrons and their ability to bind transition metallic ions (Piechowiak and Balawejder, 2019). The mechanisms of antioxidant effect can be explained by hydrogen atom transfer, single electron transfer, sequential proton loss electron transfer and transition metal chelation. During hydrogen atom transfer, phenolic antioxidant containing H atom reacts with free radicals. While the free radical is stabilised to form a neutral group, the phenolic antioxidant is converted into an antioxidant free radical. The phenolic antioxidant donates one H atom to the free radical substrate, forming a non-radical substrate group and the antioxidant free radical. The H atom donated by the antioxidant can be explained by its reduction potential (Zeb, 2020).

The mechanism of single electron transfer depends on the proton dissociation energy and ionisation potential of the reactive functional group. During single electron transfer, firstly, electron loss occurs from one molecule of the phenolic antioxidant and a cation radical is formed, while in the second step, proton loss from the phenolic antioxidant occurs. Thus, a non-radical group is formed (Antonijević et al., 2021; Platzer et al., 2021). Sequential proton loss electron transfer takes place in two stages. In the first stage, an anion group is formed as a result of the phenolic antioxidant giving a proton to a free radical. In the second stage, a non-radical group and a free radical are occured as a result of electron transfer (Najafi et al., 2011). During transition metal chelation, it has been determined that transition metals are chelated by polyphenols to form stable products. Transition metals such as copper (Cu), magnesium (Mg), cobalt (Co) can catalyse such reactions. Metal chelation can reduce the formation of reactive hydroxyl-free radicals by directly inhibiting Fe+3 reduction (Zeb, 2020).

Ferulic acid has been proven to provide antioxidant activity by hydrogen-atom transfer reaction (Berton et al., 2020). It is known that phenolic compounds obtained from scallops have antioxidant effects through the mechanisms of chelating metal ions and inhibiting lipoxygenase (Xie et al., 2019). The thermodynamics of the three mechanisms of the primary antioxidant effect of 14 phenolic acids were investigated. Hydrogen atom transfer, single electron transfer-proton transfer and sequential proton loss electron transfer mechanisms were calculated for non-polar media (benzene) and aqueous solution model. The lowest O-H bond dissociation enthalpies and bond dissociation energies for hydrogen atom transfer representing the relevant reaction pathway in both media were found for sinapic acid (Biela et al., 2022).

Mechanism of Antifungal Effect

Phenolic compounds show antifungal effect by disrupting ergosterin biosynthesis and membrane integrity of fungi. Gallic acid has been reported to show antifungal effect by inhibiting enzymes involved in ergosterol synthesis and binding to membrane ergosterol (Carvalhovd., 2018). Gallic acid also reduces ergosterol content in the filamentous fungus *Tricophytum rubrum* by inhibiting sterol 14a-demethylase and squalene epoxidase enzymes (Li et al., 2017). Tannic acid shows antifungal effect against *Penicillium digitatum* by disrupting the integrity of the cell wall and permeability of the membrane (Zhu et al., 2019). Against *Trichophyton rubrum*, quercetin causes the expression of the gene encoding an S-adenosylmethionine-dependent sterol C-24 methyltransferase in the fatty acid synthase and ergosterol biosynthetic pathway to decrease. Thus, quercetin shows antifungal effect by interfering with ergosterol synthesis and causing cell membrane disruption (Bitencourt et al., 2013). Salicylic acid shows antifungal effect against *Penicillium expansum* by damaging the conidial plasma membrane and causing soluble protein leakage (da Rocha Neto et al., 2015).

Tea polyphenols were found to exert antifungal effects by causing disruption of the synthesis of the cell wall, damage to the plasma membrane and fragmentation of hyphae and spore and induction of defence enzyme activities, and directly inhibiting hyphae growth and spore germination of *Rhizopus stolonifer* (Yang and Jiang, 2015). Flavonoids obtained from unripe bitter orange and grapefruit were observed to cause changes in the cell wall of *Aspergillus parasiticus*, retraction of cytoplasm and disruption of nuclear membranes by vesicle formation. It was determined that the flavanoids obtained showed antifungal effect against *Aspergillus parasiticus* due to severe degradation and/or loss of membranes, organelles and other cytoplasmic contents (Pok et al., 2020).

Resveratrol can induce fungal apoptosis involving mitochondrial pathways. Resveratrol, which causes metacaspase activation caused by mitochondrial dysfunction and an increase in cytochrome c release, shows antifungal effect against *Candida albicans* (Lee and Lee, 2015).

Mechanism of Antibiofilm Effect

Phytochemicals are known to have antibiofilm effect. Phytochemicals such as phenols, polyphenols, flavanones, flavonoids, flavonols are known to have quorum sensing (QS) inhibitory activities, which is a key event in the formation and development of bacterial biofilm. QS regulates the production of key virulence factors in pathogens (Nadaf et al., 2018). QS is a communication system between bacterial cells through the activation of specific signals to facilitate the adaptation of bacteria to adverse environmental conditions, including bacterial population densities. This process involves synthesising, sensing and responding to extracellular chemical signalling molecules called autoinducers (AIs). Gram-negative bacteria communicate using AIs, most commonly acyl-homoserine lactones (AHLs) or other small molecules. Phytochemicals are also involved in the inhibition of binding and deactivation of genes involved in biofilm formation (Nadaf et al., 2018).

Gallic acid and ferulic acid were understood to have antibiofilm effect against biofilms formed by *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Listeria monocytogenes*. It has been observed that these phenolic compounds have a higher inhibitory effect on biofilms formed by Gram-negative bacteria (Borges et al., 2012). Epigallocatatin gallate, a polyphenol in green tea, was found to be able to almost completely eliminate the biofilm matrix by directly interfering with the aggregation of curli subunits of the biofilm layer formed by *Escherichia coli* into amyloid fibres and reducing CsgD expression caused by CsgD mRNA targeting by triggering the σ E cell envelope stress response (Serra et al., 2016). Epigallocatatin gallate (EGCG) shows antibiofilm effect by reducing the adhesion of *Fusobacterium nucleatum* to oral epithelial cells and matrix proteins (Lagh et al., 2017).

Ellagic acid (Bakkiyaraj et al., 2013), ginkgolic acid (Lee et al., 2014), rosmarinic acid (Slobodníková et al., 2013), gallic acid, caffeic acid and chlorogenic acid (Luís et al., 2014) were understood to have antibiofilm activity against the biofilm formed by *Staphylococcus aureus*. Gallic acid affected the adhesion property of *Staphylococcus aureus*, while gallic acid and caffeic acid prevented the production of a-haemolysin of the microorganism. It has been observed that caffeic acid interferes with the stability of the cell membrane of *Staphylococcus aureus* and the metabolic activity of its cells (Luis et al., 2014). It was reported that tannic acid from black tea inhibited biofilm formation of *Staphylococcus aureus* without inhibiting bacterial growth through a transglycosylase IsaA-dependent mechanism (Payne et al., 2013). The inhibition of apigenin-7-O-glucoside on biofilm against biofilms formed by *Staphylococcus aureus* and *Escherichia coli* is carried out by inhibiting QS, exopolysaccharides and cell surface hydrophobicity (Pei et al., 2023).

Curcumin, a polyphonic compound obtained from turmeric, has been reported to have QS inhibitory activities against *Pseudomonas aeruginosa* and thus exhibits antibiofilm effect (Prateeksha et al., 2019). It was observed that cinnamic acid effectively inhibited both the production of QS-dependent virulence factors and biofilm formation against *Pseudomonas aeruginosa* PAO1. When the mechanism of antibiofilm action of cinnamic acid was examined, it was understood that it caused a decrease in biofilm development by interfering with the initial attachment of planktonic cells to the substrate (Rajkumari et al., 2018). Salicylic acid and trans-cinnamaldehyde were reported to significantly inhibit biofilm formation at sub-inhibitory levels without any bactericidal effect on the expression of QS regulatory and virulence genes in *Pseudomonas aeruginosa* PAO1 (Ahmed et al., 2019).

Protocatechuic aldehyde reduces the metabolic viability and polysaccharide production of *Vibrio parahaemolyticus*. It also inhibits cell surface flagella-mediated swimming and aggregation phenotypes. Protocatechuic aldehyde was found to have antibiofilm effect by regulating the expression of genes involved in biofilm formation of *Vibrio parahaemolyticus* (Liu and Wang, 2022).

Mechanism of Anti-oxidative Stress Effect

Oxidative stress refers to the imbalance that can damage biological systems between oxidant production and antioxidant defence (Sies et al., 2017). In other words, oxidative stress can be defined as an increase in the production of reactive oxygen species (ROS) and other oxidants that exceeds antioxidant capacity (Nakai and Tsuruta, 2021). ROS, such as free radicals, superoxide radicals, hydrogen peroxide and oxygen, refer to a range of oxygen-containing molecules and radicals produced through oxidative metabolism within mitochondria or in response to external stimuli such as xenobiotics and bacterial invasion (Taylor et al., 2022).

Polyphenols can protect against oxidative damage through various mechanisms and reduce the catalytic activity of enzymes involved in ROS formation. It has been reported that ROS formation increases free metal ions through the reduction of hydrogen peroxidase by the generation of highly reactive hydroxyl radical. Due to the low redox potentials of polyphenols and their capacity to chelate metal ions and free radicals, they can thermodynamically reduce highly oxidising free radicals (Hussain et al., 2016). It was determined that chlorogenic acid, cryptochlorogenic acid, (+)-catechin, (-)-epicatechin, procyanidin C1, procyanidin A2, rutin, quercetin, quercitrin and ferulic acid in blueberry extract have the ability to chelate Fe 2+ ion (Raudone et al., 2019).

The interaction of polyphenols with nitric oxide (NO) synthase activity may regulate NO production. Xanthine oxidase (KO) is recognised as the main source of free radicals. Some flavonoids such as apigenin, kaempferol, quercetin, silibin and luteolin may act as KO inhibitors involved in oxidative damage in tissues following such ischaemic reperfusion conditions. Flavonoids can also reduce peroxidase activity and inhibit the release of free radicals by neutrophils and the activation of these cells by α 1-antitrypsin (Sandoval-Acuña et al., 2014; Hussain et al., 2016).

The cellular enzymatic redox system (consisting of catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GR) and peroxiredoxins (PRX)) is a cellular defense mechanism that maintains the oxidative balance. This mechanism has been shown to be inadequate in cellular environments containing excessive reactive oxygen species (ROS). It has been reported that consumption or supplementation of dietary polyphenols can restore redox homeostasis and prevent systemic or localized inflammation by increasing the activities of antioxidant enzymes SOD, CAT, GPx, and GR.The expressions of these enzymes are modulated by nuclear factor erythroid (Nrf2). Nrf2 is activated and transported by reactive oxygen species; and regulates the antioxidant sensitive element-mediated transcription of genes encoding antioxidant enzymes. Dietary polyphenols can induce Nrf2 or trigger its translocation (via ligand interaction with the cytosolic aryl hydrocarbon receptor (AhR) (Zhang and Tsao, 2016). In a study examining the ability of quercetin, isoquercitrin (quercetin-3- O -glucoside), rutin (quercetin-3- O -rutinoside) and taxifolin (dihydroquercetin) to activate AhR and induce CYP1A1 expression in human hepatoma HepG2 cells, it was observed that quercetin significantly activated AhR and triggered CYP1A1 transcription after 24 hours of exposure (Vrba et al., 2021). In a study examining the ability of quercetin, isoquercitrin (quercetin-3- O -glucoside), rutin and taxifolin (dihydroquercetin) to activate AhR and induce CYP1A1 expression in human hepatoma HepG2 cells, it was observed that quercetin significantly activated AhR and triggered CYP1A1 transcription after 24 hours of exposure (Vrba et al., 2021). In another study, tangeretin 7, 12 - dimethylbenz [a] anthracene (DMBA), one of the citrus flavonoids, was found to reduce oxidative stress caused by DMBA in the liver through Nrf2 / Keap1 and AhR signaling pathways (Arivazhagan and Subramanian, 2015).

Mechanism of Anti-inflammatory Effect

Phenolic compounds could modulate gene expression through regulation of epigenetic mechanisms, including DNA methylation, histone modification or miRNA expression. In general, many phenolic compounds can activate histone deacetylases to stabilise the acetylation of histones. In addition, phenolic compounds can inhibit DNA methyltransferases, activate sirtuin genes and activate or inhibit histone acetyltransferases. Some phenolic compounds have been associated with the regulation of miRNA expression, it was determined inhibit the secretion and production of proinflammatory cytokines and reduce the production of reactive oxygen species (ROS) and nitric oxide (NO) (Číž et al., 2020).

Phenolic compounds tend to act in a complementary manner with non-steroidal anti-inflammatory drugs, but some phenolic compounds can also inhibit the activity of pro-inflammatory mediators or gene expression such as cyclooxygenase (COX). They could up- or down-regulate transcriptional elements involved in antioxidant pathways such as nuclear factor-κB (NF-κB) or nuclear factor-erythroid factor 2 (Nrf-2). Phenolic compounds are thought to suppress the binding of proinflammatory mediators, regulate eicosanoid synthesis, inhibit induced resistant units, or exert anti-inflammatory effects by inhibiting NO synthase and COX-2 activity through inhibitory effects on NF-κB (Rahman et al., 2022).

Chlorogenic acid, caffeic acid, gentisic acid and rutin have been found to exert anti-inflammatory effects by inhibiting NO production and expression of proinflammatory mediators including COX-2, tumour necrosis factor-alpha (TNF-α) and interleukin 6 (IL-6) (Choi et al., 2017). Flavonoids can reduce neuroinflammation by acting through the regulation of microglial cells. The modulatory effects induced by these compounds are mediated by their effects on important signalling pathways, including mitogen-activated protein kinases (MAPK) and NF-κB (Spagnuolo et al., 2018).

Procyanidins extracted from grape have been found to inhibit inflammatory mediators, resulting in a decrease in NO, prostaglandin E2 and ROS concentrations (Rahman et al., 2022). p -coumaric acid has been found to have a strong anti-inflammatory function by promoting a decrease in the expression of the inflammatory mediator TNF-α and circulating immune complexes (Pragasam et al., 2013).

Procyanidin B2, found in foods such as cocoa, apples, grapes or grape and cider, is a phenolic compound consisting of two flavan-3-ol (-)-epicatechin molecules. Procyanidin B2 has been associated with different anti-inflammatory effects, including modulation of various mediators of inflammation such as eicosanoids, cytokines, and NO production, as well as activation of NF-κB and mitogenesis (Martinez-Micaelo et al., 2015). Prothiandin A2 inhibits the production of cytokines and inflammatory mediators affecting related pathways such as Nrf2 signalling pathway, NF-κB and MAPK pathway (Wang et al., 2020).

It was determined that phenolic compounds in the structure of extra virgin olive oil obtained from Moraiolo olives showed anti-inflammatory effect by causing a decrease in COX-2 isoenzyme and ionised calcium binding adaptor molecule 1 (Iba-1) level. As a result of this study, it is thought that phenolic compounds may be a promising candidate for the prevention of various neuroinflammatory diseases by showing anti-inflammatory activity on brain cells (Taticchi et al., 2019).

It was determined that resveratrol and kaempferolin in the structure of lingonberry (Vaccinium vitis-idaea L.) inhibited proinflammatory M1-type activation by decreasing the expression of IL-6, NO and monocyte chemoattractant protein-1 (MCP-1) in mouse macrophages and TNF-α and IL-6 in human macrophages (Ryyti et al., 2022). Resveratol has been reported to suppress COX-2 expression and show anti-inflammatory effect when activating peroxisome proliferator-activated receptors gamma (Pparγ) and NF-κB (Dull et al., 2019).

Chlorogenic acid, rosmarinic acid and rutin found in the structure of the extract obtained from the curry leaf plant (Elsholtzia ciliata (Thunb.) Hyl.) were found to have anti-inflammatory effects by significantly reducing the secretion level of proinflammatory cytokines TNF-α, IL-6 and prostaglandin E2 induced by lipopolysaccharide treatment in mouse peritoneal macrophage cell culture (Pudziuvelyte et al., 2020).

Mechanism of Anti-obesity Effect

Phenolic compounds exert anti-obesity effects through modulation of proteins, transcriptional factors and genes involved in the digestion, energy expenditure, and metabolism of carbohydrates, increasing lipolysis, decreasing lipogenesis, stimulating B-oxidation of fatty acids, and increasing lipolysis (Oliveira et al., 2022). The phenolic extract from the fruit of Bignay (Antidesma bunius L.) has been found to exhibit a potential anti-obesity effect contributed by inhibitory effects of lipase enzyme and adipogenesis in adipocytes (Krongyut and Sutthanut, 2019).

Catechins have anti-obesity effect by means of fat oxidation, downregulation of the expression of enzymes involved in fat synthesis, upregulation of the mRNA level of fat β-oxidation genes, stimulation of sympathetic nervous system activity and increased expression of adipose tissue mismatched proteins. Many of these effects are carried out through induction of genes or inhibition of transcription factors. Catechins are also able to inhibit fat absorption through suppression of pancreatic lipase and increase the production of small absorbable metabolites that can show anti-obesity effects after absorption in the colon by correcting colonic microbiota (Akhlaghi and Kohanmoo, 2018).

The phenolic extract containing protocathequic, caffeic and ellagic acids is combined with adenosine monophosphate with the downregulation of the expression of adipogenic/lipogenic genes such as PPARy, amplifier ligands/booster binding protein-a (C/EBPa), sterol regulatory element binding protein-1 (SREBP-1), acetyl CoA carboxylase-1 (ACC1), fatty acid synthase and lipoprotein lipase-1 the receptor gamma coactivator 1-alpha activated by increasing the phosphorylation of activated protein kinase (AMPK) and by peroxisome proliferator, lipolytic genes such as sirtuin-1 (SIRT-1) and carnitine palmitoyltransferase 1-alpha and adipokine adiponectin have been reported to have an anti-obesity effect by upregulation of expression (Lin et al., 2019).

Quinic acid, caffeic acid, chlorogenic acid and 3,4-dicaffeoylquinic acid caused a decrease in serum triglyceride and low-density lipoprotein cholesterol (LDL-cholesterol) levels in obese mice fed a high-fat diet. Studies show that the anti-obesity mechanisms of action of the phenolic extract are down-regulation of C/EBPa, PPARγ and SREBP-1c to suppress adipogenesis, activating the activated protein kinase pathway, increasing ACC phosphorylation and downstream carnitine palmitoyltransferase I expression (Zheng et al., 2021).

Mechanism of Anti-diabetes Effect

Phenolic compounds have anti-diabetic effects by improving pancreatic β-cell function and improving insulin resistance, modulating various molecular targets and cell signaling pathways in hepatocytes, adipocytes and skeletal muscle cells, increasing insulin secretion (Edirisinghe and Burton-Freeman, 2016; de Paulo Farias et al., 2021). In addition, phenolic compounds also provide anti-diabetic effects through mechanisms such as AMPK pathway activation, inhibition of a glucosidase/a amylase, improvement of glucose uptake and insulin sensitivity, and PPAR activation (Deka et al., 2022).

Aldose reductase (AR), α-amylase and α-glycosidase are vital enzymes to prevent diabetic complications. Genistein has been found to have an inhibitory effect against AR and α-glycosidase (Demir et al., 2019). Quercetin, luteolin, luteolin -7 - O -glucoside, kaempferol and apigenin have a lowering effect on the insulin resistance of HepG2 cells by activating ampk (Huang et al., 2015). Curcumin prevents cell death by improving pancreatic β cell functions and thus reduces insulin resistance (Pivari et al., 2019). The anti-diabetic effect of quercetin is materialized by reducing lipid peroxidation, glucose absorption by glucose transporters-2, inhibition of insulin-dependent activation of phosphoinositide 3-kinases, stimulation of glucose uptake in muscle cells and activation of AMPK (Al-Ishaq et al., 2019). Rutin exerts anti-diabetic effects by improving glucose uptake by tissues, activating insulin secretion from pancreatic β cells, reducing carbohydrate absorption from the small intestine, suppressing tissue gluconeogenesis, and protecting islets of Langerhans (Ghorbani, 2017). In damaged pancreatic cells, Luteolin improves insulin secretion in uric acid by decreasing micro-autologous fat transcription, a trans activator of the insulin gene via the NF-κB signalling pathway, in pancreatic β cells (Ding et al., 2014).

Mechanism of Anti-ageing Effect

The biological process in which cellular organelles such as proteins, DNA and mitochondria are damaged is called aging. As a result of biochemical reactions that develop during the aging process, cell proliferation decreases, and cellular wear and tear occurs. Phenolic compounds included in diets show anti-aging effect by taking part in the prevention of cellular destruction caused by the aging process (Pyo et al., 2020).

Equol is a type of isoflavone found in soya beans and many mechanisms of action have been declared in studies to elucidate its anti-aging effect. Equol can show anti-aging effect by reducing ROS production through oxidative stress and stimulation of Nrf2. It is known that excessive ROS production damages DNA. Equol, which causes a decrease in ROS production, is also involved in the protection of DNA and the repair of nerve and tissue cells. Equol is known to inhibit activator protein-1, neoplastic cell growth, metalloproteinases, elastase and proinflammatory transcription factor (NFkappaB). Equol, which stimulates matrix metalloprotease-1, collagen, elastin and antioxidant/detoxifying enzymes, shows anti-aging effect on human skin (Lephart et al., 2016; Gong et al., 2023).

It is known that ellagic acid has a high anti-inflammatory and antioxidant effect capacity and shows anti-aging effect. Studies show that ellagic acid can reduce neuronal defects, increase neuronal vitality, and can be used in the treatment of neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and cerebral ischemia (Zhu et al., 2022). It has been understood that quercetin, myricetin, ellagic acid, gallic acid and chlorogenic acid improve the aging process, scavenging free radicals, increasing the amount of antioxidant enzymes catalase and superoxide dismutase, and decreasing the level of malondialdehyde (Wu et al., 2022).

Phenolic-containing extract obtained from two different tragacanth herbs show anti-aging effects by activating the PI3K/Akt signalling pathway, which is an important intracellular signalling pathway in the regulation of oxidative stress balance and cell cycle (Gong et al., 2021).

Mechanism of Cardiovascular Effect

Phenolic compounds are effective in the treatment of cardiovascular diseases. Dietary phenolic compounds have beneficial effects on the cardiovascular system by decreasing platelet activity, suppressing the oxidation of LDL-cholestorol, lowering blood pressure, improving endothelial dysfunction, adjusting the ratio of atherosclerotic plaque and HDL / LDL in the cardiovascular system, reducing inflammatory stress and promoting increased antioxidant effect (Lutz et al., 2019; Behl et al., 2020; Zhao and Yu, 2021). Polyphenols in blueberries and strawberries are involved in the improvement of various cardiovascular risks such as endothelial function, blood pressure, blood lipids and arterial stiffness after acute and short-term consumption (Rodriguez-Mateos et al., 2014).

Atherosclerosis is one of the main factors behind cardiovascular diseases. Phenolic compounds could inhibit important risk factors that contribute to the initiation and development of atherosclerosis, reduce oxidative and inflammatory stress. Hydroxycinnamic acid, flavanols, anthocyanidins and guaiacols exert lipid regulatory action by promoting cholesterol excretion via the small intestine or gallbladder, inhibiting lipid absorption in the small intestine and novo lipid synthesis in the liver. Activation of transcription regulators such as SIRT-1, PPAR and liver X receptor is responsible for lipid regulation (Toma et al., 2020). Caffeic acid, caffeic acid phenethyl ester and synthetic caffeic acid phenethyl amide exhibit vasorelaxant activity by acting on endothelial and vascular smooth muscle cells. Caffeic acid and caffeic acid phenethyl ester, in addition to having a vascular relaxant effect, promote a decrease in heart rate and show blood pressure lowering activity because they can suppress the renin-angiotensin-aldosterone axis (Silva and Lopes, 2020).

CONCLUSION

Phenolic compounds commonly found in plants are very important bioactive substances in terms of the quality of foods and human health. As a result of the rewieved studies, it has been found that phenolic compounds have an antimicrobial effect. When examined from the point of view of food technology, the degradation factor and the antimicrobial effect they both against pathogenic bacteria make phenolic compounds very valuable. In addition, it has been observed that these compounds also have the property of inhibiting biofilm formation, which leads to serious problems for the food industry and human health. Biofilms are polymeric layers produced by bacteria that protect bacteria against adverse environmental conditions, factors such as exposure to UV light. It has been found that the effect of anti-biofilm mechanism of phenolic compounds occurs according to inhibiting the quorum sensing process of bacteria, deactivating the genes responsible for biofilm formation and blocking binding, reducing CsgD expression, affecting the adhesion properties of bacteria, and inhibiting cell surface hydrophobicity. Phenolic compounds have been found to have antifungal activity against fungi by disrupting the biosynthesis of ergosterol and membrane integrity of fungi, damaging the plasma membrane, infiltrating soluble proteins and gene expression. The fact that phenolic compounds have antimicrobial, antifungal and antibiofilm properties allows the availability of these compounds as natural food additives. The use of these compounds as food additives is expected to replace artificial food additives in improving the quality of food, extending the shelf life of food, and ensuring food safety.

The effect of phenolic antioxidants are related to their structure and are based on the scavenging of free radicals, inhibiting of lipid peroxidation and activating of the endogenous antioxidant system. Antioxidants protect human health against various diseases by removing free radicals from the body and contribute to the development of immunity. Polyphenols have been found to have anti-oxidative stress properties against oxidative stress, which occurs because of the imbalance between reactive oxygen species and antioxidant defense and damages human health. In addition, as a result of the rewieved studies, it has been determined that phenolic compounds have a preventive effect against obesity, which has increased in recent years due to unbalanced nutrition, hormone disorder, lack of physical activity, etc.

It has been observed that some phenolic compounds exhibit anti-inflammatory effects against inflammation, which is popularly known as inflammation but includes abscesses as well as inflammation. This effect is thought to be anti-inflammatory by suppressing the binding of proinflammatory mediators by phenolics, regulating eicosanoid synthesis, inhibiting NO synthase and COX-2 activity by inhibiting stimulated units or inhibitory effects on NF-κB.

Phenolic compounds have anti-diabetic effects by improving pancreatic β-cell function, increasing insulin secretion, and improving insulin resistance. They can show anti-aging effects by reducing the production of reactive oxygen species and oxidative stress, scavenging free radicals, increasing the amount of catalase and superoxide dismutase enzymes, and reducing malondialdehyde levels. In addition, dietary phenolic compounds have been found to have beneficial effects on the cardiovascular system by reducing platelet activity, suppressing the oxidation of LDL-cholesterol, lowering blood pressure, improving endothelial dysfunction, reducing inflammatory stress, and increasing antioxidant effect.

Studies on the bioactivity of phenolic compounds generally show that they have positive properties in the protection of food quality and human health. In recent years, it hass predicted that phenolic compounds as natural additives will replace artificial additives because of their use in foods has been discussed. However, the most important issue in the use of phenolics both as additives in foods and in dietary consumption is the determination of acceptable daily intake amounts. It is seen that the bioactive properties of phenolic compounds depend on their chemical structure. For this reason, the mechanisms of bioactive effect of the phenolic compounds identified need to be fully understood.

Conflict of interest

The authors declared no conflict of interest.

Author contribution

All authors contributed equally.

Ethical Statement

During the writing process of the study titled "**Bioactive Properties and Mechanisms of Effect of Phenolic Compounds**", scientific rules, ethical and citation rules were followed; No falsification has been made on the collected data and this study has not been sent to any other academic media for evaluation. Ethics committee approval is not required.

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