

# The role of phenolic compounds as potential antimicrobial agents

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## ABSTRACT

Infectious diseases caused by pathogenic bacteria have important issue in worldwide and bacterial infections/intoxications can worsen in some people with more complex medical circumstances, such as children, elderly, pregnant women, and immunocompromised people. Antibiotics are typically used to treat these diseases. However, antimicrobial resistance in pathogenic bacteria has retained its prominence as one of the primary global health problem in recent decades. In addition to the well-known antioxidant properties of phenolic compounds, they have also inhibitory effects in pathogenic microorganisms. Due to their antimicrobial action, extracts from many fruits and vegetables with a rich phenolic compounds have been studied and promising results have been obtained. In this context, plant extracts or pure phenolic compounds can be used in the food industry as potential antibacterial agents instead of synthetic food preservatives. This chapter summarizes and discusses the phenolic compounds, classification and extraction procedure, antimicrobial activity of phenolic compounds, mechanism of action, *in vitro* studies and usage of this compounds in food system as future perspective.

**Keywords**—phenolic compounds; antimicrobial activity; pathogenity;

## I. INTRODUCTION

Phenolic compounds, which are characterized by their chemical structure containing a phenol ring and one or more hydroxyl groups, have become an important and popular research topic since the 90's due to the positive effects they provide on human health. Phenolic compounds are phytochemicals found in various plant-derived foods, including a wide variety of compounds with different chemical structures and properties [1]. To date, 8000 phenolic compounds have been identified in 16 different classes. The shikimic acid pathway and phenylpropanoid metabolism are responsible for the synthesis of phenolic compounds, a varied category of secondary metabolites that are widely distributed throughout plants. They play a variety of roles in plants, such as defense against pathogens and other invasive species, unsuitable temperature, unfavorable soil pH, UV radiation protection, and oxidative stress management. They are also responsible for the pigmentation of plants and their organoleptic (taste and odor) properties [2,3]. Beyond their importance in plant physiology, phenolic compounds have gained recognition for their potential health benefits in humans. Because of their powerful antioxidant properties, phenolic compounds have been scientifically proven to prevent various oxidative stress-related chronic diseases such as cancer, cardiovascular and neurodegenerative diseases. In addition, there are many clinical scientific studies demonstrating the anti-inflammatory, antimicrobial, anti-proliferative, anti-carcinogenic, anti-diabetic properties of phenolic compounds. In recent years, the study of phenolic compounds has expanded to include their interactions with the gut microbiota and their potential role in modulating gut health. These compounds can influence the composition and activity of the gut microbiome, with potential implications for digestion, metabolism, and immune function. In conclusion, because of their diverse functions in both plant biology and human health, phenolic compounds represent an exciting area of research. Their importance in a variety of disciplines, from agriculture and biotechnology to nutrition and medicine, is highlighted by their antioxidant, antibacterial, and possibly gut-modulating capabilities.

## II. PHENOLIC COMPOUNDS

## A. Classification

Phenolic compounds are defined as compounds with aromatic or aliphatic structures structurally and at least one aromatic ring to which one or more hydroxyl groups are attached [4]. These compounds are found in plant foods such as cereal grains, vegetables, legumes, fruits, nuts, and foods processed from these plant sources (juices, wine, tea, etc.). Phenolic compounds are classified in many different ways in the literature. According to the number of phenol units in the molecule, as flavonoids and non-flavonoids, according to the number of aromatic rings, water solubility, and carbon structure [5,6].

Phenolic compounds containing carboxylic acids are called phenolic acids. The term "hydroxybenzoic acid" refers to a carboxylic acid whose functional group is directly linked to the phenol ring; the term "hydroxycinnamic acid" refers to a carboxylic acid whose functional group and the phenol ring are separated by two double-bonded carbons. Examples of hydroxybenzoic acids are salicylic acid, m-hydroxybenzoic acid, p-hydroxybenzoic acid, gallic and vanillic acid. Plant foods contain traces of these compounds or do not contain them at all. The hydroxycinnamic acids are found more in foods compared to hydroxybenzoic acids. Ferulic acid, caffeic acid, o-coumaric acid and p-coumaric acid can be given as important hydroxycinnamic acids [7]. Although phenolic acids exist in the form of esters, glycosides or amides, they can rarely be found in free form. The variation in phenolic acids is due to the number of hydroxyl groups in the aromatic ring and the variation in placement [5].

Flavonoids are phenolic compounds that make up more than half of the more than eight thousand known phenolic compounds and are among the main polyphenols of the human diet. These compounds, together with carotenoids and chlorophyll, are responsible for the blue, purple, yellow, orange and red colors of the plant. Flavonoids consist of diphenyl propane and two benzene rings combined with a triple carbon chain. The diversity in the flavonoid structure arises from the hydroxylation, prenylation, alkalization and glycosylation reactions that change the basic molecule [5]. According to the oxidation state of the centrally located carbon ring, flavonoids are divided into 6 groups: flavanols, flavones, flavanones, flavan 3-ols, anthocyanins, and isoflavones. The main representatives of flavanols; myricetin, kaempferol and quercetin, which are abundant in leeks, broccoli and onions. Tea and red wine also contain the glycoside form of flavanols with some simple sugars such as glucose or rhamnose. The flavanols are abundant in tea, cocoa, some fruits such as apples and strawberries. Epicatechin, epicatechin gallate, and epigallocatechin gallate are examples of catechins. Flavanols are known for their antioxidant activities and have been associated with cardiovascular health benefits [8]. Flavonones such as hesperidin and naringenin are widely found in citrus fruits [9]. They have antioxidant and anti-inflammatory properties. Anthocyanins are a class of water-soluble natural pigments within a group of flavonoids abundant in plants. Anthocyanins have good antioxidant activity depending on the location and amount of hydroxyl groups in their structure, the degree of glycation and electron donors. Anthocyanins are responsible for the vibrant red, purple and blue colors in many fruits and vegetables. Well-known anthocyanin compounds include cyanidin, delphinidin, and malvidin [10]. Isoflavones such as genistein and daidzein are predominantly found in legumes, especially soybeans. Their estrogenic activity has been well-explained and are of interest for their potential health benefits, including relieving menopausal symptoms and reducing the risk of certain hormone-related cancers [11].

Lignans are formed by dimerization as a result of oxidative coupling reactions of two phenylpropanoid units. Their wide structural diversity has resulted in differences in their terminology and classification. Eight types of lignans are classified according to the carbon chain skeleton, the way oxygen is integrated into the skeleton, and the cyclization mode [12]. Lignans are commonly synthesized in flaxseed, sesame, and pumpkin. Lignans have been reported to have estrogenic and anti-estrogenic activity [7,10].

Stilbenes are a class of phenolic compounds found naturally in a wide variety of dietary sources such as grapes, strawberries, peanuts, red wine, and some herbs. But the main dietary sources are peanuts and grapes. The basic chemical structure of stilbene compounds is 1,2-diphenylethylene, and the trans form is commonly found in plants. Recently, stilbenes have attracted a great deal of attention for their wide range of health benefits, including anti-inflammatory, anticarcinogenic, antidiabetes, and antidyslipidemia activities. The main representative compound of this group is the resveratrol compound, which exerts antioxidant effects in the cardiovascular system and can reverse multidrug resistance in various tumor cells by sensitizing them to chemotherapeutic agents [7,13,14].

## B. Extraction procedure

The existence of strong scientific evidence revealing the relationship of dietary polyphenols between nutrition and health has led researchers to studies aiming to obtain these compounds from plant tissues with minimal damage. Phenolic compounds represent a very complex family of compounds, ranging from monomers such as phenolic acids to highly polymerized molecules such as tannins. In addition to this complex structure, these compounds exist in conjugated forms with one or more sugar units (monosaccharides, disaccharides, and even oligosaccharides) attached to hydroxyl groups. They can also bond with other compounds such as carboxylic acids, amines and lipids (terpenes). However, there are many parameters that affect the recovery of phenolic compounds from plant materials, such as solvent polarity, stability of compounds, sample preparation

before extraction and extraction methods. Despite numerous qualified scientific studies, a generally accepted procedure for the extraction of all phenolics or a particular group has not been established [8].

Traditionally, the extraction of phenolic compounds, especially free phenolic compounds, has been carried out using different conventional solid-liquid extraction techniques (Soxhlet, maceration, hydrodistillation, etc.) using organic solvents such as water, acetone, ethanol, methanol. Although it is known that the quantitative and qualitative performance of the extraction largely depends on the polarity of the solvent used, it varies depending on the chemical composition of the phenolic compounds to be extracted, the number and position of their hydroxyl groups, molecular size, temperature, contact time, particle size, substrate: solvent ratio, and food matrix [15].

Although traditional extraction techniques such as maceration, soxhlet extraction, decoction and percolation have simple procedures, they have disadvantages such as low extraction efficiency, long time and labor intensive requirements, high consumption of organic solvents that can be toxic and remain in the extracts in trace amounts. Due to these drawbacks, these traditional techniques have been replaced by alternative extraction methods using an energy source in recent years. These techniques, which are based on green technology, reduce energy consumption, allow the use of non-toxic, biodegradable, facility-friendly solvents that can be recovered at the end of the process, provide high efficiency and purity, and low solvent consumption. In addition to traditional extraction methods, techniques such as supercritical fluid extraction, microwave assisted extraction, ultrasound assisted extraction, pulsed electric field, pulsed ohmic heating, high pressure have started to be used in the extraction of phenolic compounds and the results are promising [16,17,18].

Solvents used to extract polyphenols include water, methanol, chloroform, n-hexane, ethanol, propanol, ethyl acetate and acetone. Differences in the polarities of these solvents cause different effects on the extraction of phytochemicals. According to studies, proanthocyanidins and tannins were best extracted with acetone, flavonoids and their glycosides with ethanol, and phenolic acids and catechin with methanol. This is explained by the higher the molecular weight of the solvent, the lower the polarity, and the easier it is to extract other substances with similar molecular weights. The polarity of acetone, ethanol and methanol is 0.355, 0.654 and 0.762, respectively. Due to low polarity of acetone is ideal for the extraction of high molecular weight phenolic compounds such as condensed tannins [19].

The use of aqueous organic solvents has better extraction efficiency compared to absolute organic solvents [8]. The effect of different solvents (ethanol, methanol and acetone) and their aqueous forms on the phenolic component extraction from a traditional Chinese medicinal plant was investigated and it was determined that the total phenolic content increased as the concentration of all three organic solvents increased in the 0-70% concentration range. However, between 70-90%, it was emphasized that the phenolic component content decreased for all three organic solvents with increasing organic solvent concentration [20].

In addition to choosing the optimum extraction solvent, time and temperature are two other important parameters that affect the yield of phenolics extracted from plant foods. In general, increasing time and temperature increases the solubility of the solute, but plant phenolics are degraded by undesirable reactions such as enzymatic oxidation due to long extraction times and high temperatures. Santos and Martins [21], in their optimization study for the extraction of phenolic compounds from edible flowers, found that the extraction of anthocyanins was most affected by the temperature parameter, while the content of phenolic compounds and flavonoids affected the recovery efficiency the most.

The solvent-to-sample ratio and the number of repeated extractions performed also affect the recovery of phenolics. It is suggested that increasing the solvent-to-sample ratio promotes the extraction of phenolic compounds from plant samples, but considering the amount of solvent and determining the optimum ratio to minimize the saturation of the solvent in terms of phenolic compounds [5].

### III. ANTIMICROBIAL PROPERTIES OF PHENOLIC COMPOUNDS

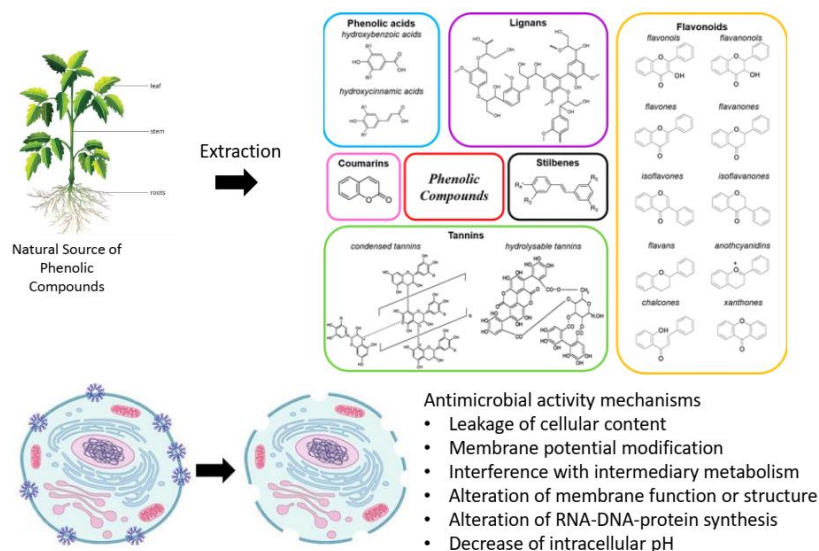
The oldest medical application of phenolic compounds is the use of phenol as an antiseptic. It has been reported that modern antiseptic agents effective against *Staphylococcus aureus* have been compared with a 5% (w/v) phenol solution, and phenol is currently used as an oral anesthetic in throat lozenges at a concentration of 1.4% [22]. The issue of microbial food safety has grown into a significant public health concern worldwide. Additionally, the emergence of multidrug-resistant bacterial strains in the food chain poses a substantial threat, reflecting the elevated risk of resistant food-borne illnesses. This concern highlighted the requirement for natural, plant-based alternatives for preserving and inhibiting bacterial growth. Phenolic compounds, have demonstrated promise not only in their antimicrobial effects but also in their potential to serve as replacements for synthetic preservatives.

#### A. The mechanisms of antimicrobial activity of phenolic compounds

Phenolic compounds exhibit antimicrobial activity through multiple mechanisms (Figure 1). One of the main mechanisms is that the microorganism disrupts cell membrane permeability. This leads to leakage of

cellular components and ultimately to cell death. This destructive effect on the cell membrane has been associated with the hydrophobic nature of phenolic compounds, which allows them to interact with lipids and proteins present in the cell membrane [23]. Also, the antioxidant properties of phenolic compounds contribute to their antimicrobial activities. The oxidative stress caused by phenolic compounds affects the growth and survival of microorganisms by damaging their DNA, proteins and lipids. In addition to these mechanisms of action, they modulate the activity of various enzymes involved in metabolism [12,24]. Many phenolic compounds such as ferulic acid, gallic acid, carvacrol, thymol and eugenol cause the deterioration of the intracellular pH of the microorganism due to the changes they create in the ion flow, and they block production by interfering with the energy production system [25]. Undissociated forms of phenolic acids, can pass through the phospholipid bilayer of bacterial membranes and lower the pH inside the cell. The disruption of DNA, RNA, and protein synthesis or functions, interference with intermediary metabolism [specifically the energy (ATP)-generating system], and coagulation of cytoplasmic constituents as a result of its acidification are all reported effects of phenolics penetrating in the cytoplasm of microorganisms [26].

Studies are presented showing that Gram-positive bacteria are more sensitive to phenolic compounds than Gram-negatives [27,28,29,30]. The phenolic compounds have mechanisms of action that play a role in antimicrobial activity such as temporary or permanent damage to cell membrane permeability, changing some functions in the cell cytoplasm and changing intracellular pH [31,26]. Cueva et al. [27] investigated the effects of thirteen different phenolic acids on 3 different *Escherichia coli* strains, *Lactobacillus* spp., *S. aureus*, *Pseudomonas aeruginosa* and *Candida albicans*. They stated that Gram-positive *S. aureus* was the most sensitive bacterium to phenolic acids, and the growth of *P. aeruginosa* was not affected in the presence of any phenolic acid at the tested dose. One of the possible mechanisms explaining the antimicrobial effect of phenolic acids against pathogens has been explained as the hyperacidification of the plasma membrane interphase as a result of the dissolution of the phenolic acids. This hyperacidification changes the cell membrane potential, making the cell membrane more permeable, and also affects the sodium-potassium ATPase pump involved in ATP synthesis. Gram-positive bacteria lack an outer membrane to prevent diffusion of phenolic acids through the cell wall, intracellular acidification, and irreversible changes in the sodium-potassium ATPase pump. On the contrary, the outer membrane of Gram-negative bacteria acts as a barrier against hyperacidification and, together with the MexE-MexF-OprN operon transport system that pumps toxins out of the cell, they are resistant to the effects of phenolic compounds. In addition, the hydrophilic nature of the outer membrane results in repelling some phenolic molecules with hydrophobic properties [26].



**Figure 1. Main antimicrobial activity mechanisms of phenolic compounds.**

## B. *In vitro* studies of phenolic-rich extracts and pure phenolics

The antimicrobial properties against several microorganisms of phenolic compounds have been demonstrated in various *in vitro* studies using polyphenol-rich extracts derived from by-products and/or waste of edible plants or pure compounds. Phenolic compounds are abundant in grapes, with the majority of it being found in the skin and seeds. The relative abundance of quercetin (26.3%), gallic acid (24.4%), protocatechuic acid (16.7%), and luteolin (11.4%) was revealed in a grape (*Vitis vinifera* L.) pomace methanol extract. With a MIC range from 0.3 to 3 mg/mL, this extract proved effective at inhibiting antibiotic-resistant *Escherichia coli* and *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA). In another study, gallic,

vanillic, syringic, p-coumaric, ellagic, and protocatechuic acids, which were present in methanol grape pomace extracts, had MIC values against *S. aureus* and *E. coli* that ranged from 0.062 to 3 and 0.2-2.5 mg/mL, respectively [24]. Zambrano et al. [32] investigated the antimicrobial activity of residual extracts of grape, apple and pitahaya and they found that the black grape sample demonstrated a stronger inhibitory impact on most bacteria than apple and pitahaya.

Bobinaite et al. [33] examined some properties of rowan pulp extracts prepared with different solvents and reported that the strongest antimicrobial activity against the tested strains was in the acetone extract. Researchers explained this situation by the fact that the acetone extract has the highest neochlorogenic acid content. In addition to neochlorogenic acid, it has been determined that there are studies that show the antimicrobial activity of quercetin and that it is a very strong antimicrobial and antiviral agent [34,35,36]. Quercetin is highly effective against some antibiotic-resistant bacteria, making it a promising phenolic compound by health authorities. It has been stated that among the antimicrobial and antiviral mechanisms of quercetin, there are mechanisms such as damaging the cell membrane, impairing membrane permeability, inhibiting the synthesis of nucleic acids and proteins, reducing the expression of virulence factors, dysfunctioning mitochondria, and preventing biofilm formation [36]. The suppression of ketoacyl carrier protein synthases, which are involved in bacterial fatty acid production, is assumed to be the main mechanism of quercetin's antibacterial effect. Quercetin has also been found to have antifungal effects. By lowering cell adhesion and influencing the genes involved in biofilm formation, quercetin works in conjunction with other antifungal medications like fluconazole and amphotericin B to fight fungus [34]. In a review, in which the use of natural plant-based antimicrobial compounds as an alternative to some synthetic food preservatives or biocides was discussed, the antimicrobial activity of many plant phenolic compounds was evaluated and it was emphasized that the use of phenolic-rich plant extracts would be beneficial for biofilm control on food contact surfaces [26].

The antimicrobial activity of phenolic compounds varies depending on their chemical structure, concentration and the targeted microorganism. Some phenolic compounds such as resveratrol and quercetin show broad-spectrum antimicrobial activity against a wide variety of microorganisms, but phenolics such as thymol and eugenol have more specific antimicrobial effects, especially against bacteria and fungi [24,25]. Fattouch et al. [37] demonstrated in their study that chlorogenic acid is a stronger antimicrobial compound than quercetin and kaempferol. Bouarab Chibane et al. [23] investigated the antibacterial activity of 35 phenolic compounds (3 stilbenes, 8 cinnamic acids, 6 benzoic acids, 11 flavonoids, 5 coumarins, and 2 naphthoquinones) against *L. monocytogenes* and five other bacteria at a concentration of 1 g/L. All examined polyphenols showed an inhibitory effect on *L. monocytogenes*, with 54.3% of the compounds showing a bacterial load differential (BLD) above 50%. The resveratrol and pinosylvin were the stilbenes that were most effective against this bacterium, with 100% and 97.9% of BLD, respectively. In a study, the antibacterial effects of curcumin, resveratrol, cinnephrene, p-coumaric acid and coniferyl alcohol on *E. coli* W1485 and *Bacillus cereus* strains were investigated and it is found that 240 µg/mL resveratrol inhibited *E. coli* W1485 in 48 hours and 240 µg/mL cinnamaldehyde inhibited *B. cereus* in 4 hours [38]. In a study, in which the structural, spectroscopic and biological activity of 5-O-caffeoylquinic acid (5-CQA), one of the main chlorogenic acids found in many fruits, vegetables and plants, was extensively investigated and the compound was tested against *E. coli*, *S. aureus*, *Enterococcus faecium*, *Proteus vulgaris*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* and *Candida albicans*. It was reported that the minimum inhibitory concentration (MIC) values were 5-10 mg/mL, and the strongest antimicrobial activity was determined against *K. pneumoniae* among the microorganisms tested [39].

Studies demonstrate that phenolic compounds have antibacterial effects on not only pathogenic bacteria but also lactic acid bacteria. However, lactic acid bacteria, fortunately, were more resistant to these substances. In a study investigating the effects of six hydroxycinnamic acids and six hydroxybenzoic acids on *Lactobacillus plantarum*, *Lactobacillus hammesii*, *Lactobacillus fermentum*, *Lactobacillus reuteri*, *E. coli* and *Bacillus subtilis*. Lactic acid bacteria were significantly more tolerant to phenolic acids than *E. coli* and *B. subtilis*. It was found that *L. plantarum* metabolized all other phenolic acids except chlorogenic acid, *L. reuteri* metabolized only chlorogenic acid, *L. fermentum* metabolized p-coumaric acid and ferulic acid. The most resistant and most sensitive bacteria in the study were associated with the fact that the antimicrobial activity of phenolic acid metabolites transformed by lactic acid bacteria was 2-5 times lower than the parent compound [40]. This study strikingly reveals that the tolerance of lactic acid bacteria to phenolic compounds is due to their ability to metabolize phenolic compounds. With a similar approach, it has been observed that lactic acid bacteria are used in sunflower flour to prevent browning caused primarily by chlorogenic acid [41]. In another study, phenolic extracts of 6 different plants, including pomegranate peel, thyme and clove, were found to contain 5 common pathogens (*B. cereus*, *E. coli*, *S. Typhimurium*, *Shigella flexneri* and *S. aureus*) and 5 common lactic acid bacteria (*L. acidophilus*, *L. delbrueckii* subsp. *bulgaricus*, *L. casei*, *L. plantarum* and *L. rhamnosus*) were investigated. The extracts inhibited food pathogens at different doses, but very high doses are required for the inhibition of lactic acid bacteria [42].

Research shows that phenolic compounds can be used as natural preservatives for food preservation due to their preventive effects against a wide variety of foodborne pathogens, including bacteria such as *E. coli* and *Salmonella* spp., as well as molds such as *Aspergillus* species. Their potent antimicrobial activities and their widespread availability in plants make phenolic compounds promising candidates for the development of new antimicrobial agents and strategies to combat infectious diseases [30,32]. Furthermore, as a result of the indiscriminate use of antimicrobial drugs, the emergence of pathogenic microorganisms resistant to certain antibiotics has increased in recent years. Antimicrobial resistance in bacterial pathogens is associated with high morbidity and mortality. Multidrug resistance patterns in Gram-positive and Gram-negative bacteria are difficult to treat and render conventional antibiotic treatments ineffective. The synergistic antimicrobial activity of the use of phenolic compounds in combination with conventional antibiotics was evaluated in the studies of Buchmann et al. [43] and Hossain et al. [44]. Study findings show that the combination of phenolic compounds with antibiotics increases antimicrobial activity against both Gram-positive and Gram-negative bacteria. This suggests that the potentially required dose of antibiotics in patients can be reduced and the development of antibiotic resistance can be minimized.

#### IV. STRATEGIES TO APPLY PHENOLIC COMPOUNDS IN FOOD SYSTEM

In recent years, the large amounts of polyphenols have been reported in most of the plant food wastes and they are a cheap source of polyphenols. Seeds, pulp and peel, which are considered as fruit waste and are by-products of the fruit processing industry, constitute 30% of the total weight of some fruits [10, 45]. The residues left after wine production correspond to 20-30% by weight of the total processed grapes and approximately 70% of the grape polyphenols remain in the pulp. It is also reported that pomegranate (*Punica granatum* L.) peels, which constitute 40% of the whole fruit and are rich in phenolic compounds, are generally seen as waste and cannot be used industrially [10]. Pulp, a by-product of the cranberry juice processing industry, has also been stated to be a good source of ellagic acid [46]. Citrus industry by-products, particularly the peels, have been found to contain higher amounts of total phenolics compared to the edible parts. The apple, peach and pear peels contain twice as much total phenolic substance as found in fruit pulp. The edible pulp of banana contains 232 mg/100 g dry weight phenolics, which corresponds to approximately 25% of the amount of phenolic substance in the peel [47].

There are numerous approaches that may be used to apply phenolic compounds. One key strategy involves utilizing phenolic-rich plant extracts as natural preservatives against food-borne pathogens. It's crucial to understand which are the most efficient for each food matrix and how they are more stable to achieve optimal food preservation. Phenolic compounds can be applied by dipping, spraying, washing, or rinsing and can be added directly to a solution as additives or dispersion agents. However, careful formulation and testing are crucial to ensure that the compounds' beneficial properties are retained while avoiding undesirable effects on taste and texture. Another strategy is to enhance the bioavailability of phenolic compounds in the human diet. This can be achieved by formulating food products in ways that improve their absorption and utilization within the body. Technologies such as encapsulation and nanoemulsions can protect phenolic compounds during digestion, ensuring they reach the target tissues intact and exert their health-promoting effects. Moreover, polyphenols can be added as an additive or incorporated into coatings or films to extend their shelf life, especially when you take into account their antioxidant properties.

Overall, integrating phenolic compounds into food systems requires a multidisciplinary approach that considers formulation, preservation, processing and regulation. By harnessing the potential of these natural compounds, the food industry can offer healthier, safer, and more sustainable products to meet the evolving demands of consumers.

#### REFERENCES

- [1] V. Silva, G. Igrejas, A. Aires, V. Falco, and P. Valente, "Phenolic compounds classification and their distribution in winemaking by-products," *Eur. Food Res. Technol.*, vol. 249(2), pp. 207-239, November 2023.
- [2] O.R. Alara, N.H. Abdurahman, and C.I. Ukaegbu, "Extraction of phenolic compounds: A review," *Curr. Res. Nutr. Food Sci.*, vol. 4, pp. 200-214, December 2021.
- [3] M.I. Dias, M.J. Sousa, R.C. Alves, and I.C.F.R. Ferreira, "Exploring plant tissue culture to improve the production of phenolic compounds: A review," *Ind. Crops Prod.*, vol. 82, pp. 9-22, April 2016.
- [4] D.L. Ambriz-Pérez, N. Leyva-López, E.P. Gutierrez-Grijalva, and J.B. Heredia, "Phenolic compounds: Natural alternative in inflammation treatment. A Review," *Cogent Food Agric.*, vol. 2(1), pp. 1-14, January 2016.
- [5] A. Khoddami, M.A. Wilkes, and T.H. Roberts, "Techniques for analysis of plant phenolic compounds," *Molecules*, vol. 18(2), pp. 2328-2375, February 2013.
- [6] T. Kılıç, "Amasya ve piraziz elma çeşitlerinin biyoaktif özelliklerinin belirlenmesi (Phd Thesis)," Çukurova Üniversitesi, Adana.
- [7] J. Gao, Z. Yang, C. Zhao, X. Tang, Q. Jiang, and Y. Yin, "A comprehensive review on natural phenolic compounds as alternatives to in-feed antibiotics," *Sci. China Life Sci.*, vol. 66, pp. 1518-1534, December 2022.

- [8] O.R. Alara, N.H. Abdurahman, and C.I. Ukaegbu, "Extraction of phenolic compounds: A review," *Curr. Res. Nutr. Food Sci.*, vol. 4, pp. 200–214, December 2021.
- [9] B. Singh, J. Pal, A. Kaur, and N. Singh, "Phenolic composition, antioxidant potential and health benefits of citrus peel," *Food Res. Int.*, vol. 132, pp. 109114, June 2020.
- [10] B.R. Albuquerque, S.A. Heleno, M.B.P.P. Oliveira, L. Barros, and I.C.F.R. Ferreira, "Phenolic compounds: Current industrial applications, limitations and future challenges," *Food Funct.*, vol. 12(1), pp. 14–29, November 2021.
- [11] D.C. Vitale, C. Piazza, B. Melilli, F. Drago, and S. Salomone, "Isoflavones: estrogenic activity, biological effect and bioavailability," *Eur J Drug Metab Pharmacokinet*, vol. 38, pp. 15–25, November 2013.
- [12] K. Ecevit, A.A. Barros, J.M. Silva, and R.L. Reis, "Preventing microbial infections with natural phenolic compounds," *Future pharmacol.*, vol. 2(4), pp. 460–498, November 2022.
- [13] Q.Z. Lv, J.T. Long, Z.F. Gong, K.Y. Nong, X.M. Liang, T. Qin, W. Huang, and L. Yang, "Current state of knowledge on the antioxidant effects and mechanisms of action of polyphenolic compounds," *Nat. Prod. Commun.*, vol. 16(7), August 2021.
- [14] Y. Zhang, P. Cai, and G. Cheng, "A brief review of phenolic compounds identified from plants: their extraction, analysis, and biological activity," *Nat. Prod. Commun.*, 17(1), January 2022.
- [15] A. Lama-Muñoz, and M. del M. Contreras, "Extraction systems and analytical techniques for food phenolic compounds: A review," *Foods*, vol. 11(22), pp. 3671, November 2022.
- [16] M.C. Bubalo, S. Vidović, I.R. Redovniković, and S. Jokić, "New perspective in extraction of plant biologically active compounds by green solvents," *Food Bioprod. Process.*, vol. 109, pp. 52–73, May 2018.
- [17] D. Huang, J. Wang, F. Li, M. Xie, Q. Qu, Y. Wang, W. Sun, C. Wu, W. Xu, R. Xiong, Y. Ding, A. Yang, and C. Huang, "Optimization of the ultrasound-assisted extraction for phenolic compounds content and antioxidant activity of Cortex fraxini using response surface methodology," *Eur. J. Wood Wood Prod.*, vol.81(3), pp. 685–697, December 2023.
- [18] K.I.B. Moro, A.B.B. Bender, L.P. da Silva, and N.G. Penna, "Green extraction methods and microencapsulation technologies of phenolic compounds from grape pomace: A review," *Food Bioprocess Technol.*, vol. 14(8), pp. 1407–1431, May 2021.
- [19] A. Mokrani, and K. Madani, "Effect of solvent, time and temperature on the extraction of phenolic compounds and antioxidant capacity of peach (*Prunus persica* L.) fruit," *Sep. Purif. Technol.*, vol. 162, pp. 68–76, April 2016.
- [20] Y. Ma, J. Chen, D. Liu, and X. Ye, "Ultrasonics sonochemistry simultaneous extraction of phenolic compounds of citrus peel extracts: Effect of ultrasound," *Ultrason. Sonochem.*, vol. 16(1), pp. 57–62, January 2009.
- [21] L.G. Santos, and V.G. Martins, "Optimization of the green extraction of polyphenols from the edible flower *Clitoria ternatea* by high-power ultrasound: A comparative study with conventional extraction techniques," *J. Appl. Res. Med. Aromat. Plants*, vol. 34, pp. 100458, April 2023.
- [22] W. Vermerris, and R. Nicholson, "Phenolic compound biochemistry". In *Phenolic Compound Biochemistry* Springer Science and Business Media. 2006 pp. 1–34.
- [23] L. Bouarab-chibane, V. Forquet, P. Lantéri, and Y. Clément, "Antibacterial properties of polyphenols: Characterization and QSAR (Quantitative Structure – Activity Relationship) models," *Front. Microbiol.*, vol. 10, pp.829, April 2019.
- [24] M.C. Lima, C.P. De Sousa, C. Fernandez-prada, J. Harel, J.D. Dubreuil, and E.L. De Souza, "A review of the current evidence of fruit phenolic compounds as potential antimicrobials against pathogenic bacteria," *Microb. Pathog.*, vol. 130, pp. 259–270, May 2019.
- [25] S. Zamuz, P.E.S. Munekeata, C.K.O. Dzuvor, W. Zhang, A.S. Sant, and M. Lorenzo, "The role of phenolic compounds against *Listeria monocytogenes* in food. A review," *Trends Food Sci. Technol.*, vol. 110, pp. 385–392, April 2021.
- [26] N. Oulahal, and P. Degraeve, "Phenolic-rich plant extracts with antimicrobial activity: an alternative to food preservatives and biocides?," *Front. Microbiol.*, vol. 12, pp. 3906, January 2022.
- [27] C. Cueva, M.V. Moreno-arribas, P.J. Martín-Alvarez, G. Bills, M.F. Vicente, A. Basilio, C. Rivas Lopez, T. Requena, J. M. Rodriguez, and B. Bartolome, "Antimicrobial activity of phenolic acids against commensal, probiotic and pathogenic bacteria," *Res. Microbiol.*, vol. 161(5), pp. 372–382, June 2010.
- [28] I. Dimkić, P. Ristivojevi, T. Janakiev, T. Beri, J. Trifkovi, D. Milojković-Opsenica, and S. Stanković, "Phenolic profiles and antimicrobial activity of various plant resins as potential botanical sources of Serbian propolis," *Ind. Crops Prod.*, vol. 94, pp. 856–87, December 2016.
- [29] R.S.Govardhan Singh, P.S. Negi, and C. Radha, "Phenolic composition, antioxidant and antimicrobial activities of free and bound phenolic extracts of *Moringa oleifera* seed flour," *J. Funct. Foods.*, vol. 5(4), pp. 1883–1891, October 2013.
- [30] T.C.S.P. Pires, M.I. Dias, L. Barros, M.J. Alves, M.B.P.P. Oliveira, C. Santos-Buelga, and I.C.F.R. Ferreira, "Antioxidant and antimicrobial properties of dried Portuguese apple variety (*Malus domestica* Borkh. cv Bravo de Esmolfe)," *Food Chem.*, vol. 240, pp. 701–706, February 2018.
- [31] W. Khochapong, S. Ketnawa, Y. Ogawa, and N. Punbusayakul, "Effect of *in vitro* digestion on bioactive compounds, antioxidant and antimicrobial activities of coffee (*Coffea arabica* L.) pulp aqueous extract," *Food Chem.*, vol. 348, pp. 129094, June 2021.
- [32] C. Zambrano, E.B. Kerekes, A. Kotogán, T. Papp, C. Vágvölgyi, J. Krisch, and M. Takó, "Antimicrobial activity of grape, apple and pitahaya residue extracts after carbohydrase treatment against food-related bacteria," *LWT - Food Sci. Technol.*, vol. 100, pp. 416–425, February 2019.
- [33] R. Bobinaitė, C. Grootaert, J. Van Camp, Š. Antanas, M. Liaudanskas, V. Žvikas, P. Viškelis, and P. Rimantas Venskutonis, "Chemical composition, antioxidant, antimicrobial and antiproliferative activities of the extracts isolated from the pomace of rowanberry (*Sorbus aucuparia* L.)," *Food Res. Inter.*, vol. 136, pp. 109310, October 2020.
- [34] M. Azeem, M. Hanif, K. Mahmood, N. Ameer, F.R.S. Chughtai, and U. Abid, "An insight into anticancer, antioxidant, antimicrobial, antidiabetic and anti-inflammatory effects of quercetin: A review," *Polym. Bull.*, vol. 80(1), pp. 241–262, January 2023.
- [35] M.T. Gatto, S. Falcocchio, E. Grippa, G. Mazzanti, L. Battinelli, G. Nicolosi, and L. Saso, "Antimicrobial and anti-lipase activity of quercetin and its C2-C16 3-O-acyl-esters," *Bioorg. Med. Chem.*, vol. 10(2), pp. 269–272, February 2002.
- [36] T.L.A. Nguyen, and D. Bhattacharya, "Antimicrobial activity of quercetin: An approach to its," *Molecules*, vol. 27(2494), pp. 1–13, April 2022.
- [37] S. Fattouch, P. Caboni, V. Coroneo, C.I.G. Tuberoso, A. Angioni, S. Dessi, N. Marzouki, and P. Cabras, "Antimicrobial activity of tunisian quince (*Cydonia oblonga* Miller) pulp and peel polyphenols extracts". *J. Agric. Food Chem.*, vol. 55(3), pp. 963–969, January 2007.

- [38] S. Makwana, R. Choudhary, J. Haddock, and P. Kohli, "In-vitro antibacterial activity of plant based phenolic compounds for food safety and preservation," *LWT-Food Sci. Technol.*, vol. 62(2), pp. 935–939, July 2015.
- [39] E. Bajko, M. Kalinowska, P. Borowski, L. Siergiejczyk, and W. Lewandowski, "5-O-Caffeoylquinic acid: A spectroscopic study and biological screening for antimicrobial activity," *LWT-Food Sci. Technol.*, vol. 65, pp. 471–479, January 2016.
- [40] A.F. Sanchez-Maldonado, A. Schieber, and M.G. Ganzle, "Structure – function relationships of the antibacterial activity of phenolic acids and their metabolism by lactic acid bacteria," *J. Appl. Microbiol.*, vol. 111(5), pp. 1176–1184, November 2011.
- [41] C. Fritsch, V. Heinrich, R.F. Vogel, and S. Toelstede, "Phenolic acid degradation potential and growth behavior of lactic acid bacteria in sun flower substrates," *Food Microbiol.*, vol. 57, pp. 178–186, August 2016.
- [42] C. Chan, R. Gan, N.P. Shah, and H. Corke, "Polyphenols from selected dietary spices and medicinal herbs differentially affect common food-borne pathogenic bacteria and lactic acid bacteria," *Food Control*, vol. 92, pp. 437–443, October 2018.
- [43] D. Buchmann, N. Schultze, J. Borchardt, K. Schafler, and S. Guenther, "Synergistic antimicrobial activities of epigallocatechin gallate , myricetin , daidzein , gallic acid , epicatechin , methoxyflavone and genistein combined with antibiotics against ESKAPE pathogens," *J. Appl. Microbiol.*, vol. 132(2), pp. 949–963, February 2022.
- [44] A. Hossain, H. Park, S. Park, S. Park, and M. Seo, "Synergism of the combination of traditional antibiotics and novel phenolic compounds against *Escherichia coli*," *Pathogens*, vol. 9(10), pp. 811, October 2020.
- [45] R.F. Dibanda, E.P. Akdowa, and Q.M. Tongwa, "Effect of microwave blanching on antioxidant activity, phenolic compounds and browning behaviour of some fruit peelings," *Food Chem.*, vol. 302, pp. 125308, January 2020.
- [46] S. Martins, S.I. Mussatto, G. Martínez-Avila, J. Montañez-Saenz, C.N. Aguilar, and J.A. Teixeira, "Bioactive phenolic compounds: Production and extraction by solid-state fermentation. A review," *Biotechnol. Adv.*, vol. 29(3), pp. 365–373, May-June 2011.
- [47] N. Balasundram, K. Sundram, and S. Samman, "Phenolic compounds in plants and agri-industrial by-products: Antioxidant activity, occurrence, and potential uses," *Food Chem.*, vol. 99(1), pp.191–203, 2006.