

Polyphenols as a new class of prebiotics for gut microbiota manipulation

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Abstract

A thriving community of microorganisms resides in our intestines, forming complex interactions and producing signaling molecules that can affect human physiological processes. Intrinsic and environmental factors modulate the composition of the microbial ecosystem, with diet representing a key factor affecting the formation of gut microbiota. The epidemic of non-communicable chronic diseases has been associated with the Western diet, which may modulate the gut microbiota, resulting in a detrimental derangement in the microbial community, termed dysbiosis.

Dysbiosis may be reverted through dietary interventions and the application of probiotics and prebiotics. Phenolic compounds represent plant-based nutraceuticals, which can be separated into phenolic acids and polyphenols, that exert prebiotic-like effects and may prevent the development of diseases. Besides direct health-promoting activities, beneficial effects of phenolic compounds may be exerted through their interaction with the gut microbiota. A bidirectional relationship between the gut microbiota and phenolic compounds has been observed, as microorganisms are involved in the metabolism of phenolic compounds, whereas phenolic compounds may affect the composition of the microbiota, with selective stimulatory or inhibitory activity towards the growth of microbial members. In this review, insight into the gut microbiota-polyphenols relationship will be given, with a focus on the application of polyphenols for modifying microbiota and promoting health.

Key words: polyphenols, microbiota, prebiotic, quorum-sensing

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Introduction

More than 2000 years ago, Hippocrates postulated that “all disease begins in the gut”, indicating that even in ancient ages people knew about the importance of healthy intestines. However, only in recent years did it become apparent that the community of microbes residing in the gastrointestinal tract and their function are important for maintaining health and promoting disease. Microorganisms reside in and on our bodies, and the most diverse microbial ecosystem, termed gut microbiota, is present in the gastrointestinal tract. Human intestines are colonized by more than 100 trillion microorganisms, with distal parts of the colon characterized by the highest diversity and density of microorganisms (1, 2).

The recent advantages in microbiota analysis methods, along with the improvements in culture-based methods, provided an important insight into the complex composition and activity of the human microbiota (3-6). Human gut microbiota contains over 1000 bacterial species, several hundreds of fungi species, and several thousands of viruses and other microorganisms. Today, with the application of advanced sequencing methods combined with various bioinformatics tools, it is possible to study this ecosystem with species or even strain-level resolution (3, 7-9).

Microorganisms residing in the intestines are involved in various functions, including catabolism of nutrients and xenobiotics, synthesis of vitamins, as well as the maintenance of intestinal barrier integrity and resistance to pathogen colonization. Moreover, microbial metabolites may enter the circulation and exert effects on distal organs. Through their activity, gut microbiota affects human metabolic pathways responsible for energy balance, appetite control, immune function, cardiometabolic and neurobehavioral processes (1, 10, 11).

Gut microbiota is a dynamic ecosystem, which is affected by intrinsic and environmental factors during its formation. Throughout life, gut microbes are under the influence of acute or long-term perturbations – such as diet changes, treatment with antibiotics or other medications, the existence of gastrointestinal pathologies, level of physical activity, pregnancy, type of delivery and breastfeeding, and different environmental exposures, among others (2, 12). Among all these factors, diet represents a major factor in the modification of the microbial ecosystem. Diet provides necessary nutrients for humans, but it also provides substrates for microbial growth. In addition, many microbial species are ingested through diet. Differences in dietary patterns significantly shape the microbiota of each individual (13-16). Unfortunately, the industrialization and mass production of ultra-processed food contributed to the development of the dietary style prevalent in most of the world. This Western diet is characterized by a high intake of saturated fats, simple sugars, sodium, and a deficient intake of essential micronutrients, phytochemicals, and complex plant carbohydrates, as shown in Figure 1 (17, 18). The Western diet, combined with the irrational use of antibiotics, pesticides, and other chemicals, has led to the great extinction of microbial species that used to colonize the human gastrointestinal tract for centuries. Differences in

gut microbiota composition between urban and rural populations are remarkable, and urbanized populations have significantly lower microbial diversity, with a higher abundance of pathogenic species (19-21).

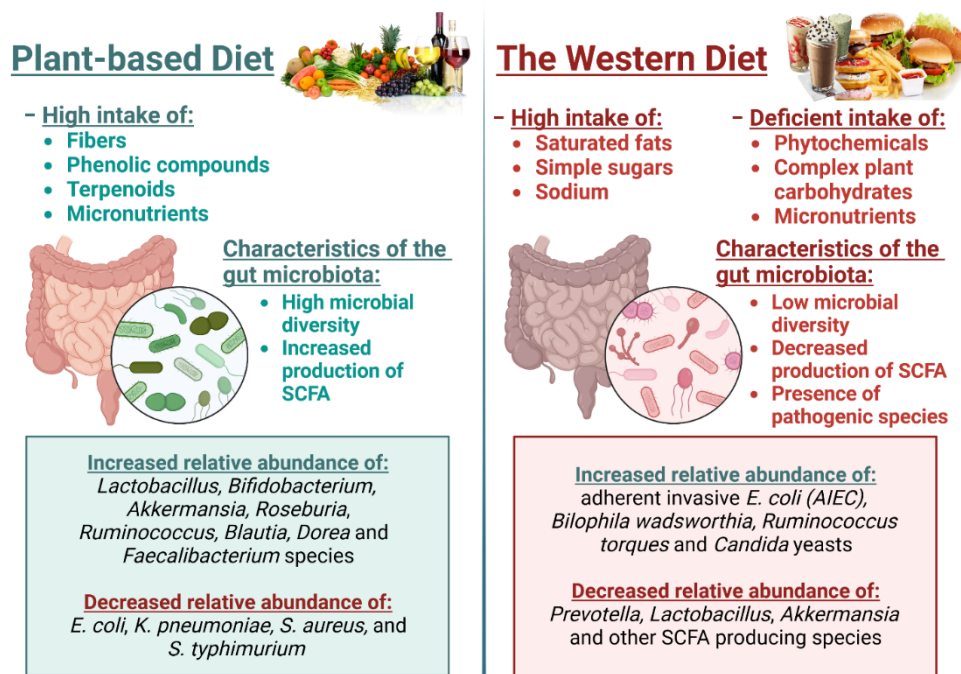


Figure 1. Comparison of plant-based and Western diet in nutrients and phytochemicals intake, and the composition of the gut microbiota

Slika 1. Poređenje ishrane zasnovane na namirnicama biljnog porekla i zapadnjačkog načina ishrane u unosu nutrijenata, fitohemikalija i sastavu mikrobiote

Under the persistent and/or intense influence of stressors, a detrimental derangement in the structure and function of microbial communities, termed dysbiosis, may occur. Dysbiosis, characterized by low diversity, loss of beneficial microbial species, and colonization of potential pathogenic microorganisms, is associated with various proinflammatory diseases, from local gastrointestinal pathologies, to cardiometabolic, neurologic, respiratory, and immune-related disorders, indicating the importance of maintaining the integrity of the intestinal microbial ecosystem (22-24). The epidemic of non-communicable chronic diseases is probably linked to microbiota dysbiosis, while the low effectiveness of traditional therapies most likely reflects the fact that we are underusing the ability to modify microbiota in a desired direction. Microbiota modification is possible through dietary and functional medicine interventions, including dietary changes, and the use of probiotics, prebiotics, or synbiotics (25-28).

Since its introduction in 1995, the term prebiotic has changed its definitions with new evidence regarding the prebiotic activity of various food compounds (22, 29, 30). Previously, prebiotic potential was associated with non-digestible carbohydrates, and to

be defined as prebiotics, substances had to meet three criteria, including resistance to gastric acidity, hydrolysis by mammalian enzymes and gastrointestinal absorption, being fermented by intestinal microbiota, and selectively stimulating the growth and/or activity of intestinal bacteria associated with health (30). According to the most recent definition of the International Scientific Association for Probiotics and Prebiotics (ISAPP), prebiotics are defined as substrates selectively utilized by host microorganisms and conferring a health benefit. Besides focusing not only on specific bacterial species, but on the entire microbiota, the latest definition encompasses the beneficial activity of prebiotics not only in the gastrointestinal tract, but also in other parts of the body (22, 31).

In addition to the well-established prebiotics from the group of non-digestible polysaccharides and oligosaccharides such as β -glucans, inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), recent studies have shown that non-carbohydrate molecules may also exert prebiotic activity. These molecules include polypeptide polymers, poly-unsaturated fatty acids, polyphenols, and other phytochemicals (1, 32). As of 2016, ISAPP has included polyphenols as a potential class of prebiotics, as the health-promoting activities of polyphenols have been shown to be mediated through their interaction with the gut microbiota (22). In this review, we discuss the possibilities of using polyphenols as a tool for modifying microbiota composition and function to promote health.

Phenolic acids and polyphenols

Phenolic compounds represent a chemically diverse group of phytochemicals, widely distributed in fruits, vegetables, herbs, spices, and beverages, such as wine, tea, and cocoa. More than 8,000 phenolic compounds have been identified. These secondary plant metabolites are involved in the regulation of plant development and protection against reactive oxygen species (ROS), ultraviolet radiation, and pathogens (1, 23, 33).

The classification of phenolic compounds varies according to different criteria, with several existing classifications based on the chemical structure (34). Phenolic compounds may be broadly divided into simple phenols, phenolic acids and their derivatives, and more complex polyphenols (35-37). The main constituent of phenolic compounds is an aromatic ring with at least one hydroxyl group. Phenolic acids possess one carboxylic acid group and can be separated, based on the length of the chain containing the carboxylic group, into hydroxybenzoic, hydroxycinnamic acids, and other hydroxyphenyl acids, including acetic, propanoic, and pentaenoic (35). Polyphenols possess one or more aromatic rings that have more than one hydroxyl group and can be divided into flavonoids and non-flavonoid compounds (38, 39). Flavonoids are a diverse class of low-molecular-weight polyphenols consisting of two phenyl rings connected through a heterocyclic pyrane ring and forming a phenyl benzopyran skeleton. Based on the differences in the pyran ring, flavonoids can be further separated into six groups, including flavones, flavonols, flavanones, isoflavones, flavan-3-ols, and anthocyanidins. Among different flavonoid classes, compounds differ in hydroxylation and methylation patterns of phenyl rings, which are generally mono, di, or trihydroxylated (1, 35, 36, 40).

Non-flavonoid phenolic compounds are characterized by more complex and heterogeneous structures, and they include lignans, stilbenes and tannins, among others (39, 41). Tannins can be subdivided into hydrolysable (gallotannins and ellagitannins), condensed and complex tannins. Gallotannins and ellagitannins contain gallic acid units, whereas condensed tannins consist of catechin units and are also called proanthocyanidins. Stilbenes and lignans possess a similar structure, as stilbenes contain two phenol units linked by two double bonded carbons, whereas in lignans the phenol units are connected by four carbons (36).

Polyphenols and phenolic acids are naturally found predominantly in glycosylated forms, bound to sugar constituents as O-glycosides, and C-glycosides, and except flavan-3-ols and proanthocyanidins, they only exceptionally appear in deconjugated form of aglycones. Some flavonoids form complex oligomeric and polymeric structures, such as proanthocyanidins or condensed tannins, including procyanidins, prodelphinidins, or propelargonidins (41, 42).

The consumption of phenolic compounds varies significantly among different populations and age groups, as it is highly correlated with dietary patterns. The estimated daily intake of polyphenols in Europe varies from 500 mg to 2 gr/day, with coffee, tea, and fruit representing the main sources of phenolic compounds. Other major dietary sources include vegetables, wholegrains and nuts, cocoa, herbs and spices, and the different sources of phenolic compounds are shown in Figure 2 (43, 44). Among fruits, berries, cherries, plums, and apples have the highest amounts of polyphenols, whereas artichokes, onions, olives, and spinach represent vegetables that are an excellent source of polyphenols (45, 46).

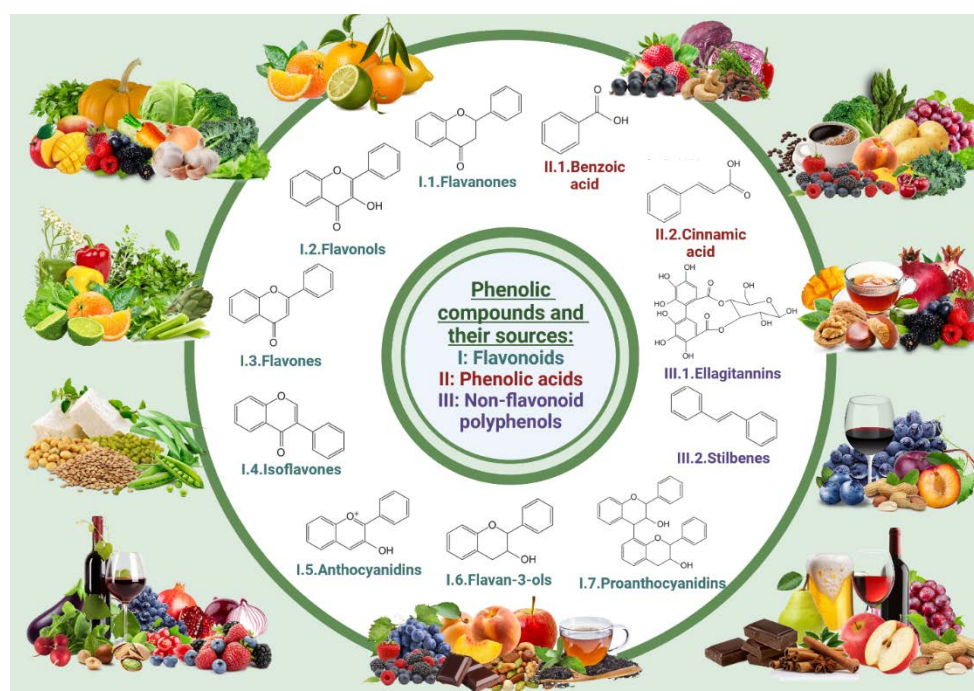


Figure 2. Classification of phenolic compounds and their sources in nature

Slika 2. Klasifikacija fenolnih jedinjenja i njihovi prirodni izvori

Medicinal plants and spices, traditionally used in culinary recipes and/or for prevention and therapy of diverse pathologies, have been identified as a rich source of phenolic compounds, with many yet unresearched phytochemicals that may possess significant biological activity. Frequently isolated phenolic compounds in culinary spices and medicinal herbs include chlorogenic, caffeic, isovanilic, and cichoric acids, kaempferol, luteolin, apigenin, and their derivatives and glycosides (47-50).

Resveratrol, curcumin, quercetin, rutin, genistein, daidzein, naringin, hesperidin, ellagitannins, and proanthocyanidins represent the most studied polyphenols with many suggested biological activities (51). Quercetin and its glycosides are among the most widely consumed polyphenols, mainly found in onions, pepper, tea, red wine, berries, pomegranates, and apples. Due to its abundance and health-promoting effects, quercetin has been thoroughly researched, resulting in many quercetin supplements currently available on the market (42). Likewise, resveratrol, a stilbenoid found in the skin of grapes, berries, peanuts, wine, and chocolate, has attracted significant attention regarding its beneficial effects on cardiometabolic parameters and cancer prevention (52). Another frequently consumed flavonoid is epigallocatechin gallate (EGCG), flavan-3-ol esterified with gallic acid, which is the main phenolic compound in green tea (~ 50% of total green tea polyphenols). Studies have revealed the high antioxidant activity of EGCG, and the ability to modulate the molecular signaling pathways through which it exerts anti-inflammatory, anti-proliferative, and other beneficial effects (53-55).

Metabolism of polyphenols

The majority of ingested polyphenols are not absorbed in the small intestine. It has been estimated that about 90-95% of consumed polyphenols reach the colon intact. In the colon, polyphenols undergo extensive biotransformation by intestinal microorganisms. Although phenolic compounds have low bioavailability, through gut microbiota-mediated metabolism, an array of metabolites is produced, which may have greater bioaccessibility and significant biological activity, and which may be responsible for the positive effects of polyphenols on health (23, 51, 56). As most phenolic compounds in plants are conjugated with sugars and organic acids and need to be hydrolyzed before absorption, the bioavailability and bioactivity of polyphenols largely depend on the metabolic capability of intestinal microbes. Gut microbiota possesses glycosidases and esterases responsible for the deconjugation of glycosides, glucuronides, and organic acids, which leads to the hydrolysis of glycosides. The released aglycones are further transformed into various derivatives through the activity of microbial enzymes involved in dehydroxylation, reduction, decarboxylation, demethylation, and isomerization reactions, among others (23, 41, 42, 57).

The catabolic pathways of phenolic compounds are complex and highly dependable on the composition and metabolic potential of the gut microbiota. As a result of polyphenol catabolism, various end products can be produced by different microbial species. In addition, the metabolism of specific phenolic compounds also depends on other factors, including the number, type, and position of specific functional groups,

polymerization degree, and stereoisomerism (41, 56). Therefore, both the nature of polyphenols and the metabolic potential of the microbiota define the type of polyphenol transformation in the colon.

Only a few of the metabolic pathways involved in the microbiota-mediated biotransformation of polyphenols have been described. One of the most thoroughly investigated is the biotransformation of soy isoflavones daidzein and genistein into equol or O-desmethylangolensin. Equol possesses more potent bioactivity compared to its precursors. Several bacterial species, including *Slackia isoflavoniconvertens*, *S. equolifaciens*, and *Adlercreutzia equolifaciens*, can produce equol from daidzein. It has been shown that the presence of these microorganisms is essential for the beneficial effects of soy isoflavones (41, 58). Likewise, the metabolism of ellagic acid and ellagitannins into urolithins (3,4-benzocoumarin derivatives) was found to be dependent on the gut microbiota composition, with several *Gordonibacter* and *Ellagibacter* species possessing tannin acyl-hydrolase enzymes necessary for the metabolism of ellagic acid (59).

Despite the presence of a few illustrative examples, due to the great structural diversity, the catabolism of polyphenols is still under-researched, and more studies are necessary to identify produced metabolic intermediates and end-products (41).

Activities of polyphenols

Similar to the diverse functions that polyphenols have in plants, results from *in vitro* and *in vivo* studies suggest that phenolic compounds possess a wide range of biological activities, which appear to be associated with the maintenance of human health and the prevention of chronic diseases (60). As mentioned earlier, medicinal plants, in addition to spices, are the richest sources of polyphenols. Medicinal plants have been traditionally used for the treatment of various gastrointestinal diseases, including gastritis, inflammatory bowel disease, and irritable bowel syndrome, among others. The positive effects of medicinal plants can largely be attributed to the presence of polyphenols. Likewise, the consumption of food rich in polyphenols has been inversely associated with the risk of the development of various non-gastrointestinal diseases, including cardiometabolic (type 2 diabetes mellitus, atherosclerosis, coronary heart disease, non-alcoholic fatty liver disease, metabolic syndrome, and others) and neurodegenerative diseases (Alzheimer's disease and multiple sclerosis), several types of cancer, other inflammatory and immune-related disorders (37, 43, 61).

The beneficial effects of phenolic compounds have usually been explained by their potent antioxidative properties; however, a plethora of other health-promoting activities have been associated with the consumption of polyphenols and phenolic acids, including anti-inflammatory, antimicrobial, anticarcinogenic, neuroprotective, antiadipogenic and immunomodulatory activities, among others (62-64). Although *in vitro* studies have proven a remarkable free-radicals scavenging activity, the *in vivo* antioxidant activity of phenolic compounds is not solely based on the free radicals elimination, as it involves the regulation of the activity of endogenous antioxidant enzymes and more complex

molecular mechanisms associated with the modulation of gene transcription and cellular signaling pathways (43).

The ability to reduce tissue inflammation has been documented for many phenolic compounds, and the effects of polyphenols on the maintenance of the gut barrier integrity have been observed in studies (1, 61). Moreover, studies have shown that polyphenols can bind to specific proteins, such as kinases associated with the regulation of pro-inflammatory cytokines (transcription factor NF- κ B, interleukin-6 (IL-6), and IL-1), and mitogen-activated protein kinase 2 (MAP kinase 2), subsequently affecting the expression of genes associated with inflammation, cell adhesion, antioxidant defense, and cell signaling (43, 62, 65-67). Results also indicate that polyphenols may alleviate chronic oxidative cellular and DNA damage, in addition to recent findings suggesting the involvement of polyphenols in the regulation of cell cycle processes and the ability to induce apoptosis by modulating mitochondrial functions and bioenergetic control (53, 68).

In addition to the direct effects on human health, polyphenols and their metabolites exert modulatory effects on the gut microbiota, affecting the composition and activity of present microorganisms. More than a decade ago, the existence of a bidirectional relationship between polyphenols and the gut microbiota was indicated, and the importance of a highly diverse microbiota for adequate polyphenol metabolism was emphasized (41, 64, 69).

Polyphenol - gut microbiota - host axis

The bidirectional interaction between polyphenols and gut microbiota has been researched using *in vitro* and *in vivo* approaches, including batch culture fermentations and gastrointestinal simulators, as well as animal model and human intervention studies (13). Polyphenols may alter the composition and activity of intestinal microbes by directly modulating the metabolic activity of microorganisms, or by exerting growth-stimulating or growth-inhibiting effects on the gut microbiota members. Reciprocally, the microbiota is involved in the biotransformation of phenolic compounds into metabolites, which may be responsible for the health-promoting properties of polyphenols and phenolic acids (58).

As the effects of consumed polyphenols are highly dependent on the gut microbiota, a great inter-individual variability in response to polyphenols is explained by the differences in microbial activity and composition. Moreover, some microorganisms require polyphenols as a nutrient source and prefer carbohydrates attached to the phenolic compounds, explaining the role of microorganisms in the biotransformation of glycosylated polyphenols. In addition to glucose, other sugar moieties, including rutinoid and neohesperidoside, may be attached to phenolic compounds and act as a preferred energy source for certain microbial species (41, 43).

Considering the high interindividual variability in gut microbiota composition and activity, the beneficial effects of ingested phenolic compounds have been inconsistent across studies, resulting in the need for tailored prebiotic interventions based on an

individual's microbiota profile. A personalized microbiota-focused approach has been investigated, with some authors investigating the possibility of categorizing individuals into metabotypes, based on variations in the microbial metabolism of phenolic compounds. By classifying individuals into producers and non-producers of certain phenolic metabolites, a personalized polyphenol-rich diet may be tailored to support a unique gut microbiota, with the goal of promoting health and treating specific diseases (41, 70, 71).

Prebiotic effects of phenolic compounds

Due to a great diversity of phenolic compounds, the effects of ingested polyphenols and phenolic acids on the growth of microorganisms vary significantly. However, several commensal species have been frequently observed to be stimulated by polyphenols. Interestingly, the utilization of polyphenols has been paralleled with the increase in the production of health-promoting short-chain fatty acids (SCFAs). Polyphenols exert prebiotic effects by modulating the gut microbiota through complex interactions with microorganisms, and they have a unique ability to promote the growth of commensal microorganisms, in parallel with the inhibition of pathogen growth (41, 64).

Studies have shown that polyphenols exert prebiotic effects through the selective growth stimulation of beneficial microorganisms, including species belonging to the genera *Lactobacillus*, *Bifidobacterium*, *Akkermansia*, *Roseburia*, *Ruminococcus*, *Blautia*, *Dorea* and *Faecalibacterium* (13, 63, 72). For example, stimulatory effects on the growth of *Lactobacillus*, *Akkermansia*, and *Ruminococcus* species were observed after the intake of orange juice, rich in hesperidin and naringenin (73). Likewise, the intake of anthocyanin-rich fruits (red and purple berries, red grape, pomegranate, and plums) promoted the growth of *Akkermansia muciniphila*, a mucin-degrading bacteria associated with beneficial effects on the integrity of the intestinal barrier, anti-inflammatory activity and protection against obesity and cardiometabolic diseases (74). In addition to anthocyanins, other phenolic compounds, including phenolic acids, flavan-3-ols, flavonols, flavanones, stilbenes, and hydrolyzable tannins, were associated with the increased abundance of *A. muciniphila* (58, 75). Supplementation with pomegranate extract, rich in ellagitannins, was found to stimulate the growth of *A. muciniphila* in urolithin A producers. Additionally, pomegranate consumption increased the abundance of several bacterial genera including *Butyrivibrio*, *Enterobacter*, *Escherichia*, *Lactobacillus*, *Prevotella*, *Serratia*, and *Veillonella*, whereas the abundance of *Collinsella* significantly decreased following dietary intervention (76).

In addition to selectively stimulating the growth of probiotic and commensal species, polyphenols have been found to have potent inhibitory activity against the growth of many pathogens and opportunistic pathogens. Phenolic compounds exert antimicrobial activity through several mechanisms, including metal-chelating ability (flavan-3-ol) and the disruption of cell membrane function, or by altering the membrane permeability (anthocyanins), antiadhesive activity (resveratrol), inhibition of biofilm formation and quorum sensing (23, 41, 42).

For instance, naringenin, quercetin, and rutin were found to inhibit the growth of *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhimurium*, whereas quercetin also exerted inhibitory activity towards the growth of *Klebsiella pneumoniae* and *Proteus vulgaris* (1).

The anti-adhesion effect of cranberry, rich in proanthocyanidin-A – procyanidin A2 and cinnamtannin B1, as well as other flavonoids and phenolic acids, on the growth of *E. coli*, represents a well-known antimicrobial effect of polyphenols, and many cranberry supplements were formulated targeting the *E. coli* urinary tract infection (UTI). In addition to suppressing the growth of *E. coli*, cranberry extracts were found to exert antimicrobial activity towards the growth of other microorganisms responsible for UTIs, including *K. pneumoniae*, and some Gram-positive staphylococci and enterococci, indicating the great potential of polyphenols in restoring microbiota balance (77, 78). Likewise, green and black tea polyphenols were found to inhibit the growth of pathogen bacteria, including *S. aureus*, *E. coli*, *Helicobacter pylori*, *S. typhimurium*, *Listeria monocytogenes*, and *Pseudomonas aeruginosa*, as well as several viruses such as hepatitis C virus, influenza, and HIV, but also *Candida* yeasts (79).

Resveratrol intake has been associated with an increase in the relative abundance of *Bacteroides*, *Lactobacillus*, *Christensenella*, *Bifidobacterium*, and *Akkermansia* (80-82). In addition to the growth-stimulating effects, resveratrol also possesses antibacterial activity against several clinically important microbial species, including *E. coli*, *Enterococcus faecalis*, and *Salmonella enterica* (81).

Similarly, the consumption of mango, rich in gallotannins and gallic acid, has been associated with selective antimicrobial activity against gram-positive bacteria, such as *Bacillus subtilis* and *S. aureus*, with beneficial effects on the growth of probiotic and/or SCFA-producing microbial species, including bifidobacterial and lactobacillus, *A. muciniphila* and butyrate-producing bacteria *Faecalibacterium* spp. and *Clostridium butyrium* (83).

Investigation of the prebiotic effects of several medicinal herbs, including willow gentian (lat. *Gentiana asclepiadea*), St John's wort (lat. *Hypericum perforatum*), winter savory (lat. *Satureja montana*), and yarrow (lat. *Achillea millefolium*), showed the selective growth stimulation of probiotic lactobacilli and probiotic yeast *Saccharomyces boulardii*, in parallel with the antimicrobial activity towards the growth of *E. coli*, *S. aureus*, *L. monocytogenes*, *P. aeruginosa*, and *Candida* yeasts (84). Moreover, the prebiotic effect of baicalin, a flavone glycoside found in root extracts from *Scutellaria baicalensis*, a traditionally used plant in Chinese medicine, was found to be exerted through the selective stimulation of growth of *Streptococcus* and *Bifidobacterium* species, with parallel inhibition of pathogenic bacteria growth, such as *H. pylori*, *E. coli* and *S. aureus* (23, 66, 85).

In addition to compositional changes, polyphenols also modulate the metabolic activity of the microbiota. Phenolic compounds influence the production of organic acids, including lactate and SCFAs. The fact that polyphenol intake leads to increased levels of

SCFAs is of particular importance, since SCFAs have several important functions in the gut, including maintenance of epithelial barrier integrity, provision of necessary nutrients, and immunomodulation (72, 86). Moreover, some polyphenols, such as quercetin, galangin, and fisetin, were found to increase the production of anti-inflammatory molecules, while the consumption of anthocyanins and ellagic acid was associated with the reduction in plasma lipopolysaccharide levels. The health-promoting effects of polyphenols can be summarized by their stimulation of SCFAs and anti-inflammatory molecules production, with the parallel inhibition of the synthesis of proinflammatory molecules (1, 72).

Quorum sensing and phenolic compounds

Phenolic compounds impact microbial growth by various mechanisms. In addition to the unique property of these compounds to stimulate beneficial and inhibit pathogenic microorganisms, their ability to interfere with quorum sensing signaling might be of major importance.

Quorum sensing is an important mechanism of communication between unicellular microorganisms, which impacts their metabolism. Although each cell is independent, microorganisms are capable of conducting coordinated activity. The possibility of group functioning has many advantages, and it allows microorganisms to, e.g., migrate towards more favorable environmental conditions, or to adapt to new growth modes such as sporulation or biofilm formation (87). Microorganisms can respond to changes by modifying their phenotype, while mutual interactions are based on the expression of quorum sensing (QS) dependent genes (88). Quorum sensing involves the production, detection, and response to extracellular molecules called autoinducers. Autoinducers accumulate in the environment when microbial population density increases, and microorganisms monitor this information to detect changes in cell numbers and collectively alter gene expression (89). When cell density increases, accumulation of autoinducers inside and outside the cell occurs, leading to the specific activation of transcriptional regulatory proteins by binding to them (90). Many important functions relevant to pathogenic phenotypes, such as toxin production or biofilm formation, are QS-dependent. Thereby, interference with QS signaling can impact the activity of particular members of an ecosystem and the ecosystem as a whole.

Phenolic compounds can impact microbial growth in various manners. In addition to growth inhibition or stimulation, phenolics can block quorum sensing, which consequently changes microbial mobility, adhesion properties, and the ability to express factors relevant to microbial virulence (91). It has been shown that grape and apple extracts, as well as various phenolic compounds, including syringic, gallic and vanillic acid, (+)-catechin, and resveratrol, can inhibit quorum sensing in a laboratory test on model organism *Chromobacterium violaceum* CV026, as well as inhibit the formation of biofilms of pathogens *L. monocytogenes*, *S. aureus*, *E. coli*, *S. enterica*, *P. putida* and *P. aeruginosa* *in vitro*, at concentrations of 100 µg/ml (92). Anti-QS effects have been proven for various polyphenols, including naringenin, quercetin, taxifolin, and

apigenin (93). Interestingly, a significant effect on QS-dependent functions can be achieved even at concentrations lower than the minimum inhibitory concentration (94). Although it is not completely clear how polyphenols interfere with QS signaling, it seems that polyphenols do not affect the production or degradation of autoinducers, but they rather make complexes with signaling molecules or interfere with their receptors (95, 96). These results indicate that polyphenols can induce modifications of ecosystem function even without the elimination or stimulation of the ecosystem members.

Conclusion

Studies have shown that polyphenols may exert beneficial effects by directly affecting human physiological functions and indirectly, by modulating the gut microbiota composition and activity and preserving the balance of the gut microbial ecosystem. Although the results indicate a positive effect of polyphenol intake on the gut microbiota, it is still necessary to clarify the exact mechanisms through which beneficial effects are exerted, as they are not seen in all individuals. In addition to the impact of the selected study design, genetic, physiological, and lifestyle differences between participants, the great discrepancy in results can also be attributed to a high inter-individual variability in microbiota structure and activity, as a complex bidirectional interaction between phenolic compounds and gut microbiota influences the effects of polyphenol intake. However, polyphenols represent a unique group of prebiotics that can interfere with molecular signaling and thereby impact the phenotype of members of the microbiota, boost the growth of beneficial and suppress the growth of pathogenic species. These properties make polyphenols an extremely interesting group of health-affecting phytochemicals, especially in relation to microbiota-mediated health effects. Given the complexity of both microbiota and polyphenols, their interaction needs to be thoroughly researched, and exciting findings could be expected to emerge from this research.

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Polifenoli kao nova klasa prebiotika za manipulaciju crevne mikrobiote

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Kratak sadržaj

Raznovrsna zajednica mikroorganizama kolonizuje naš intestinalni trakt, u kom formira složene interakcije i proizvodi signalne molekule koji mogu uticati na ljudske fiziološke procese. Unutrašnji faktori i faktori životne sredine utiču na obrazovanje strukture mikrobnog ekosistema. Mešu njima, ishrana predstavlja ključni faktor koji utiče na formiranje crevne mikrobiote. Epidemija nezaraznih hroničnih bolesti povezana je sa zapadnjačkim načinom ishrane koji može negativno uticati na crevnu mikrobiotu i uzrokovati stanje disbioze.

Dijetarnim intervencijama i primenom probiotika i prebiotika moguće je ponovo uspostaviti ravnotežu u strukturi mikrobiote. Fenolna jedinjenja, koja predstavljaju biljne nutraceutike i mogu se podeliti na fenolne kiseline i polifenole, ispoljavaju prebiotski efekat i mogu sprečiti nastanak brojnih patologija. Pored direktnih pozitivnih dejstava na stanje čoveka, efekti fenolnih jedinjenja mogu se ostvariti i kroz njihovu interakciju sa crevnom mikrobiotom. Nedavno je uočen dvosmerni odnos između crevne mikrobiote i fenolnih jedinjenja, u kom su mikroorganizmi uključeni u metabolizam fenolnih jedinjenja, dok fenolna jedinjenja mogu uticati na strukturu mikrobiote selektivnom stimulativnom ili inhibitornom aktivnošću prema rastu mikrobnih članova. U ovom preglednom radu biće dat uvid u povezanosti crevne mikrobiote i fenolnih jedinjenja, sa fokusom na primenu fenolnih jedinjenja u cilju modifikacije crevne mikrobiote i održavanja zdravlja.

Ključne reči: polifenoli, mikrobiota, prebiotici, *quorum sensing*
