



Mutual influence of polyphenols and *Lactobacillus* spp. bacteria in food: a review

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Abstract

This paper presents the effect of polyphenols on microorganisms inhabiting the human gastrointestinal tract (mainly bacteria belonging to the *Lactobacillus* genus) and pathogenic microorganisms classified as the most common food contaminants. Plant secondary metabolites have the ability to modulate the growth of many microorganisms. Due to the metabolic changes induced by their presence in the environment, many pathogenic microorganisms are unable to grow, which in turn cause a significant reduction in their pathogenic potential. These processes include primarily the induction of ruptures in the cell membrane and disturbance of cell respiration. Often, the lack of integrity of cell membranes also leads to the disturbance of intracellular homeostasis and leakage of cellular components, such as proteins, ATP molecules or intracellular ions. Autoxidizing polyphenols also act as pro-oxidative substances. Hydrogen peroxide formed in the process of oxidation of polyphenolic compounds acts as a bactericidal substance (by induction of DNA breaks). With regard to intestinal microbiota, polyphenols are considered prebiotic substances that increase the number of commensal bacteria. They can positively influence the growth of *Lactobacillus* bacteria, which have the ability to metabolize undigested antioxidants in the digestive tract of humans and animals. Depending on the pH of the environment and the presence of ions, plant polyphenols in the human digestive tract can act as substances with antioxidant potential or become pro-oxidants. Thus, combining functional food with polyphenols and *Lactobacillus* bacteria not only protects food products against the development of undesirable and pathogenic microbiota, but also has a positive effect on human health. The paper also describes the possibility of changes in the genome of *Lactobacillus* bacteria (under the influence of polyphenols) and the influence of *Lactobacillus* spp. bacteria on the antimicrobial properties of polyphenols. The enzymatic abilities of bacteria of the genus *Lactobacillus*, which influence the transformation of polyphenolic compounds, were also described.

Keywords Polyphenols · *Lactobacillus* · Antimicrobial activity · Lactic acid bacteria

Introduction

Polyphenols, as secondary metabolites of plants, comprise a large group of organic compounds. Their numerous properties, including their antioxidative and antimicrobial (against fungi and bacteria) activity, have been examined by scientists in various fields of science, i.e. medicine, biochemistry, epidemiology and pharmacy [1]. These compounds are particularly abundant in leguminous plants, nuts, cereals,

vegetables and fruit. Animal bodies are not capable of synthesizing polyphenols. Instead, they obtain them entirely from the consumption of foods of plant origin [2]. The basic division of polyphenols is based on their molecular structure, i.e. the number of aromatic rings included in their structure. Moreover, this division is based on the types of bonds present between consecutive rings. From this division, four main polyphenol classes, i.e. phenolic acids, stilbenes, lignans and flavonoids (catechins, flavones, isoflavones, flavanones, flavanols, anthocyanins) have been derived [3].

The structure of polyphenols makes it possible to distinguish among them low-molecular (phenolic acids) and high-molecular weight (tannic acids) compounds. Owing to their varied structure, polyphenols demonstrate various physical, biological and chemical properties [4]. The structure of polyphenols, based on active phenolic hydroxyl

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groups (up to a few groups in a single molecule), gives them antioxidative properties, and has considerable influence on their ability to neutralize free radicals [5]. A polyphenol's activity depends largely on the number of hydroxyl groups included in an individual molecule [6].

Antagonistic activity of polyphenols

Polyphenols possess a broad range of antagonistic activity towards pathogenic microbiota. For example, polyphenols isolated from tea are able to limit the multiplication of such pathogens as *Staphylococcus aureus*, *Salmonella* Enteritidis, *Serratia marcescens* and *Cronobacter sakazakii* [7–9]. However, during tests performed by Tabasco et al. [10] it was determined that a mixture of catechin, epicatechin and flavan-3-ol, in concentrations of 0.25–1.0 mg/ml, is capable of inhibiting the development of such pathogenic species as *Staphylococcus aureus*, *Streptococcus pyogenes*, *Staphylococcus epidermidis* and *Enterococcus faecalis*. Piekut [11] demonstrated that lovage extracts rich in anisic, cinnamic, ferulic, sentisic, syringic and *p*-coumaric acids, after 24-h incubation, inhibited the multiplication of *Escherichia coli* by 93% and *Staphylococcus aureus* by 87%. On the other hand, a 48-h culture in the presence of the extract resulted in the inhibition of the development of *Pseudomonas aeruginosa* and *Bacillus subtilis* bacteria, as well as *Candida albicans* yeast by over 90%. Moreover, thyme extract rich in anisic, gallic, sentisic, caffeic, *p*-coumaric, syringic and vanillic acids inhibited the multiplication of only two pathogenic bacterial strains, *Staphylococcus aureus* and *Escherichia coli*. Following a 48-h incubation period, the multiplication of the above-mentioned bacteria was reduced by over 80%.

The basic feature of polyphenols (and their metabolites) responsible for their impact on microorganisms is their chemical structure, including the substituents on the phenolic ring. These features result in the fact that, depending on their concentration, polyphenols can act both as activators and inhibitors of bacterial multiplication and development [12].

Bacterial cell wall integrity disruption by polyphenols

The results of current studies show a clear tendency for Gram-positive bacteria to be much more susceptible to the presence of polyphenols than Gram-negative bacteria [13]. It is believed that Gram-negative bacteria are able to be more resistant to the bactericidal activity of polyphenols due to the structure of their cell walls and the arrangement of their external membranes. This resistance results from the fact that the Gram-negative bacteria structure includes periplasmic space which is not present in Gram-positive bacteria.

Moreover, the periplasmic space is rich in enzymes capable of degrading compounds demonstrating antimicrobial potential, permeating to the external environment [14]. The external membrane of Gram-negative bacteria cells is rich in lipopolysaccharides, creating a barrier that is practically impermeable for lipophilic molecules. Active components are able to bond with the cell surface in order to be subsequently transported inside. The effectiveness of polyphenols consists in reaching the target location, i.e. phospholipid cell membranes, or in altering the synthesis of intracellular compounds, i.e. enzymes, ATP or intracellular proteins [15]. In most cases, polyphenols demonstrate a hydrophobic character, because of which they readily interact with the lipid layer located in the bacterial cytoplasm membrane. Owing to their integration with the double lipid layer of the cytoplasm membrane, polyphenols greatly disturb its stability [16]. This disruption occurs because phenolic acids are capable of causing irreversible changes in cell membrane structures and disturbing their hydrophobic properties. They are also able to induce spot ruptures compromising the impermeability of structures. Pores created in this manner become locations for the permeation of cellular material into the environment [17]. The deformation of a cell membrane's physical structure caused by the presence of polyphenols may result in the membrane swelling, which in turn results in structural instability and increased passive permeability [18]. As a result of cell membrane loosening, apart from ATP, a bacterium cell is deprived of ions, nucleic acids and amino acids which are necessary for its existence [19] (Fig. 1).

Impact of polyphenols on bacterial virulence

As regards certain pathogens (even those counted as Gram-negative bacteria) that colonize the human body (e.g. *Escherichia coli* that cause urinary system infections), some polyphenols, such as flavone-3-ol (condensed tannic acid), are able to disturb the expression of genes that are necessary to synthesize *p*-fimbriae proteins. As a result of the molecule conformation change, *Escherichia coli* bacteria are deprived of their ability to adhere to the epithelium surface [20]. When uropathogenic *Escherichia coli* bacteria do not

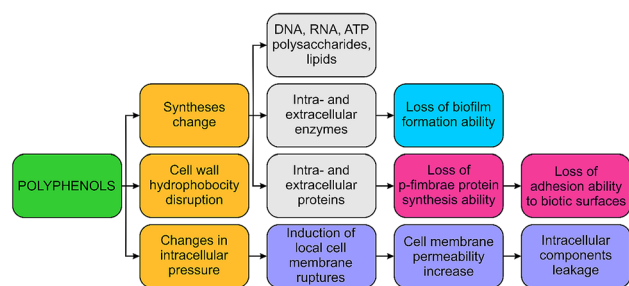


Fig. 1 Mechanism of the antimicrobial activity of polyphenols

have the ability to bond adhesively with receptors located on the host's membranes, no infection of the mucilaginous epithelium surface and subsequent development of bacterial infection can occur. Plant polyphenols with antimicrobial properties often become a factor that limits the occurrence of bacterial biofilm. Proanthocyanidins (PAC) from cranberry extract inhibit the generation of fructosyl transferase and glucose transferase. Inhibition of the activity of the above-mentioned enzymes ensures that the *Streptococcus* genus is unable to generate biofilm dependent on sucrose, which results in it being unable to settle on biotic surfaces (e.g. dental plaque). Additionally, PACs derived from cranberry are also able to inhibit biofilms whose generation does not depend on sucrose concentration. Changes in bacterial cell co-aggregation, caused by an increase in the hydrophobic nature of cell walls and modifications on their surface, prevent accumulation of bacterial cells into larger aggregates [21]. It is believed that polyphenols may have properties which alter the adhesion of pathogenic cells (including *Escherichia coli*) to human epithelium walls. Phytocompounds may influence the host's cells analogously to competitive receptors and make it impossible to create receptor–ligand bonds (common in the case of urinary system infections) [22]. Alteration of pathogenic cell adhesion in the presence of polyphenols is also visible in *Helicobacter pylori*. Derivatives of flavan-3-ol demonstrate anti-adhesive properties in relation to the bacteria, which cause inflammation of the stomach mucous membranes [23].

Alterations of bacterial metabolism caused by polyphenols

One of the bactericidal properties of polyphenols is the ability to make alterations on the level of extra- and intracellular proteins. Polyphenols isolated from sugar beet are able to disturb the synthesis and expression of genes responsible for the synthesis of proteins in *Staphylococcus aureus*, *Escherichia coli*, *Listeria monocytogenes* and *Salmonella Typhimurium*. During an experiment performed by Chen et al. [24], SDS-PAGE analysis demonstrated changes in the level of intracellular proteins for the above-mentioned bacterium species. Due to the increase in the permeability of the cell membranes of these bacterial species, more than 80% of all intracellular proteins were detected in the cell-free supernatant. This proves that polyphenols significantly affect the integrity of bacteria cell membranes. By causing their destabilization, they contribute to the death of bacterial cells. In addition, the above-mentioned experiment also proved that polyphenols penetrating the cell membranes of *Escherichia coli* affect the expression of bacterial genes coding intracellular proteins. The photo of the gel after SDS-PAGE shows the loss of the ability to synthesize many intracellular proteins in *Escherichia coli* in culture with the

addition of polyphenols from sugar beet molasses (at a concentration of 10 mg/ml). These studies confirm the results obtained by Zhao et al. [25], who presented the effect of sugar cane polyphenols on changes in intracellular protein content in food contaminating bacteria (*Escherichia coli*, *Listeria monocytogenes*, *Staphylococcus aureus* and *Salmonella Typhimurium*). A similar effect was also observed by Wang et al. [26] after adding *Listeria monocytogenes*, *Escherichia coli* and *Salmonella Enteritidis* lactic acid bacteria to the culture. Lactic acid penetrating inside the bacterial cells affects the physiology and morphology of bacterial cells, causing their degradation. The result of this experiment was also confirmed by tests conducted by Zeng et al. [27]. Moreover, polyphenols are able to damage the structure of intracellular proteins. It is supposed that the fairly rapid process of the decrease in intracellular protein concentration is caused by changes in the metabolism of energy. Changes in protein concentration also induce rebuilding of the cytoplasm membrane and membrane protein structures [28]. The antimicrobial potential of polyphenols mostly results from changes in the intracellular concentration of ATP. Changes in ATP concentration are connected with the depolarization of cell membranes, whose disturbed structure causes leakage of cytoplasm (increase in cell membrane permeability) and loss of the ATP molecules necessary for existence [29].

Antioxidative activity of polyphenols

Antioxidants are substances which, at a low concentration with respect to an oxidizing substrate, significantly delay or prevent the oxidation of other compounds by this substrate [30]. In the context of biological processes, the mechanism of the action of antioxidants is more complex and depends on more factors. Antioxidant properties may be based on inhibition of enzymes that produce oxidants or chelation of metal ions mediating oxidation reactions. There may also be a situation in which the antioxidant is oxidized instead of the substrate [31].

During aerobic respiration, bacteria produce oxygen (O_2) which is necessary for the production of cellular energy. In the case of incomplete reduction of O_2 in the process of cellular respiration, it is possible to generate reactive oxygen species, with particular emphasis on hydrogen peroxide (H_2O_2) and hydroxyl radicals (OH^\cdot). The system of bacteria protection against reactive oxygen species (ROS) is related primarily to their ability to synthesize specific enzymes such as catalase and superoxide dismutase. The addition of polyphenols to bacterial culture usually induces cell lysis, which results in an increase in the production of ROS and H_2O_2 , which results in cell death [32].

Research on the mechanisms of the antimicrobial activity of polyphenols led to the conclusion that this phenomenon may be associated with the high antioxidant potential of

these compounds [33]. Antioxidants such as polyphenols are capable of inducing physicochemical and structural changes in microorganisms, thus significantly delaying their growth [34].

To date, two basic mechanisms of the antimicrobial action of polyphenols related to their antioxidant activity have been proven. First of all, by direct production of H_2O_2 and reduction of Fe^{3+} ions to Fe^{2+} (Fenton reaction), they participate in the formation of strong, reactive oxygen species (such as hydroxyl radicals). Nevertheless, a key factor in determining whether antioxidants have antimicrobial properties is the pH value [35].

Hydrogen peroxide is produced by the oxidation of phenolic compounds such as gallic acid, (–)-epigallocatechin, (–)-epigallocatechin gallate, (+)-catechin, quercetin, hydroxytyrosol, delphinidin and rosmarinic acid. H_2O_2 (in a concentration above 100 μM) is also produced in media with the addition of catechins from green and black tea, coffee or wine. Polyphenols are also able to induce synthesis of hydrogen peroxide in beverages. In studies conducted by Grzesik et al. [31], the most active antioxidants include polyphenols such as propyl gallate (PG), pyrogallol, (–)-epigallocatechin gallate (EGCG) and quercetin (Q). Hydrolysis of hydrogen peroxide, during which oxygen is produced, significantly accelerates the processes of self-oxidation of polyphenols (with simple structures, e.g. coumarin). The antimicrobial activity of polyphenols is possible owing to the loss of antioxidant properties and transformation into a pro-oxidant (a substance that generates free radicals). According to the research carried out by Dai, Mumper [36], it is precisely under conditions favouring self-oxidation (high pH with a simultaneous high concentration of transition metal ions) that polyphenols are transformed into pro-oxidants. Moreover, hydrogen peroxide is a factor necessary to accelerate the process of self-oxidation of polyphenols (through hydrolysis). It is also a source of hydroxyl radicals. The concentration of polyphenols is the primary factor responsible for their antimicrobial properties resulting from the synthesis of hydrogen peroxide. Polyphenols alone cannot induce direct breaks in bacterial DNA. It is H_2O_2 that disrupts the integrity of the DNA strands [37]. It is believed that hydrogen peroxide, formed in the processes of self-oxidation of polyphenolic compounds (contained in plant extracts and honey), induces DNA strand breaks by accelerating oxidation processes (especially guanine) [38]. The antimicrobial properties of polyphenols may also result from their ability to interact chemically with H_2O_2 . As a result of these reactions, products responsible for the degradation of bacterial DNA are formed [39]. Pro-oxidative polyphenols may cause changes in the expression of bacterial proteins. As a result of interaction with polyphenols in bacteria more susceptible to oxidative stress, DNA damage (as a result of the breakdown of DNA fragments) and, consequently, abnormal

transcription processes occur. On the other hand, incorrect transcription can lead to disturbances in the production of superoxide dismutase and catalase (as in the case of damage caused by H_2O_2). An increased concentration of H_2O_2 can lead to transcriptional disturbances, as a result of which the genes encoding proteins synthesized during oxidative stress or the genes responsible for enzymes that properly metabolize antioxidants are damaged. A weakened bacterial cell is unable to develop properly, which often leads to its death [40]. On the other hand, while polyphenols continue to function as antioxidants, they may interact with proteins found in the bacterial cell walls. This often leads to the initiation of ionic and hydrogen bonds. Typically, these combinations induce changes in protein activity and a decrease in bacterial resistance. It should be remembered that the antioxidant activity of polyphenols also changes [40]. The mere presence of polyphenols in the growth environment of bacteria (due to their antioxidant potential) causes oxidative stress [35]. Hydrogen peroxide generated by the auto-oxidation of polyphenols may also have an effect not only on microorganisms, but also on cells. Grzesik et al. [31], in studies on DU-145 (human prostate carcinoma) cells, investigated the cytotoxicity of PG, EGCG and Q. The results of their research show that the cytotoxicity of polyphenols is much lower in tests with the addition of catalase (an enzyme that decomposes hydrogen peroxide). Thus, it is likely that the negative impact on cells should not be attributed to polyphenols, but to products formed in the process of their self-oxidation.

It is worth emphasizing, however, that the antioxidant activity (and thus the antimicrobial activity) of polyphenols may depend on many factors. The ability to absorb free radicals depends primarily on the pH of the environment, metal reduction potential, solubility, or activity of chelating polyphenols. The antioxidant properties of polyphenols are observed in systems where plant metabolites use redox active metals (iron, copper) [41, 42].

In studies conducted by Grzesik et al. [31], during the incubation of 54 different substances with antioxidant potential (incubation: 3 hours, 37 °C), as many as 27 antioxidants (mainly natural food ingredients) produced hydrogen peroxide. The kinetics of H_2O_2 synthesis was linear. The highest concentration of hydrogen peroxide was recorded in the initial phase of incubation (after about 1.5 h). Among the tested antioxidant substances, the highest concentration of H_2O_2 in the culture media was observed in the case of propyl gallate (PG), (–)-epigallocatechin gallate (EGCG) and quercetin (Q). In these studies, it was also observed that another antioxidant (not derived from plants) may have an influence on the course of antioxidant processes and the production of H_2O_2 . Ascorbate in the environment reduced the production of hydrogen peroxide by 60% for Q and inhibited the production of H_2O_2 for PG and EGCG. The production of reactive

oxygen species for these compounds also depended on light. However, it is not a universal mechanism. In the case of exogenous compounds, incubation in the dark does not weaken the processes of auto-oxidation and the formation of hydrogen peroxide. In the context of microbial culture, it is worth mentioning that the formation of hydrogen peroxide may depend on the composition of the medium. The amount of H_2O_2 formed as a result of self-oxidation of polyphenols varies significantly in Dulbecco's modified Eagle's medium (DMEM), DMEM supplemented with L-glutamine, or in phosphate-buffered saline (PBS). As a result of PG, EGCG and Q self-oxidation, 110–127 $\mu\text{mol } H_2O_2$ was formed in PBS medium, while in DMEM with additional L-glutamine between 41.8 and 157.9 μmol . There are also substrates such as yeast extract peptone dextrose (YPG) in which polyphenols such as EGCG and Q are not oxidized, and thus no hydrogen peroxide is generated. The resulting reactive oxygen species are sometimes the result of the integration of polyphenols with the organic components of the substrate, which initiate the processes of self-oxidation of polyphenols. It is worth remembering that the culture media may be contaminated with transition metal ions. Thus, the amount of hydrogen peroxide formed may also be influenced by the water used to prepare the microbial medium. Tea solutions were tested by Grzesik et al. [31], made using water directly from the tap and based on deionized water. It turned out that in tea based on tap water the concentration of the formed H_2O_2 was kept at the level of 85 μM , while in the case of deionized water it was only 25 μM . It should be emphasized that the level of contamination with transition metal ions in the culture medium and the water used in the reaction will always be a factor influencing the rate of self-oxidation of polyphenols. It will also indirectly influence the ability to form ROS, and thus it will be a factor influencing the speed of the bactericidal activity of polyphenols.

Unfortunately, in the literature there is no clear correlation between the synthesis of hydrogen peroxide and the chemical structure of polyphenolic compounds. It is presumed that compounds with a simple structure undergo faster autooxidation. It is environmental factors that have a much greater impact on the amount of H_2O_2 synthesized in the oxidation of polyphenols. Transition metal ions in particular are responsible for catalysing the self-oxidation of compounds with antioxidant potential. From an industrial point of view, it is the contamination of finished products with various transition ions that can have a significant impact on their antioxidant properties. Moreover, polyphenols undergo self-oxidation processes faster, the higher the pH of the environment. For example, ascorbic acid in a solution at a concentration of 10 mM (used as a control for substances with antioxidant potential) generates small amounts of H_2O_2 . By neutralizing the solution to pH 7.0, the amount of H_2O_2 formed is much higher. Thus, the self-oxidation of

polyphenols depends on the pH of the environment. It is assumed that in the human intestine this process may occur much faster than in other sections of the gastrointestinal tract [31, 43]. Therefore, polyphenols may show pro-oxidative activity and inhibit the growth of bacteria in slightly alkaline environments (pH 7.0–8.0) [37].

In their research, Taleb et al. [40], also observed that the osmolarity of date syrup (related to the high sugar content in the syrup) does not have a significant effect on the auto-oxidative activity of polyphenols.

The low concentrations of polyphenols found in plants usually behave as antioxidants, thus, when combined in a nutritional matrix with *Lactobacillus* spp. bacteria, they can fulfil a protective function [40].

Honeydew honey is an example of a product containing a large amount of phenolic acids and flavonoids, having antioxidant and pro-oxidative properties. The antibacterial activity of honeys (mainly honeydew, less often nectar) is attributed to high concentrations of polyphenols, which may be involved in the production of increased amounts of H_2O_2 [44, 45].

According to research by Bucekova et al. [37], honeydew honey has the ability to inhibit the multiplication of both Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli*) bacteria. However, these properties are more noticeable in Gram-positive bacteria. Thus, in 40% (w/v) solutions of the tested honeydew honeys, the content of hydrogen peroxide was determined after 24-h incubation at 37 °C. The samples contained between 0.3 and 3.4 mM H_2O_2 , and the average value of the H_2O_2 concentration in the tested samples of honeydew honey was 1.8 mM. Out of 23 tested samples, only two were characterized by poor H_2O_2 production (less than 1 mM). The total polyphenol content was also determined using the Folin–Ciocalteu method in 20% (w/v) honey solutions. Results are expressed as GAE equivalent (mg/ml) using gallic acid (GAE) as standard. In the tested honey samples, no direct participation of polyphenolic compounds in the antibacterial potential of honey was demonstrated (despite the high content of polyphenols: 30–60 mg GAE/100g honey). However, it has been recognized that phenolic compounds may act synergistically through pro-oxidative effects (producing increased levels of H_2O_2). Thus, Bucekova et al. [37], to confirm the participation of H_2O_2 in the antibacterial effect of honeydew honey, subjected 50% (w/v) honey solutions to a 2-h catalase treatment. Samples treated with catalase had lower antimicrobial activity with mean MIC values of 30%, which is evidence that supports the above thesis. According to research by Poli et al. [46], hydrogen peroxide formed as a result of auto-oxidation of polyphenols contained in honey acts as a killer against *Pseudomonas aeruginosa* bacteria. In order to confirm their thesis, the authors of the above-mentioned study also conducted additional studies. An experiment was

carried out in which the hydrogen peroxide in the culture medium was neutralized by adding catalase (1000 U/ml; 2 h). Thus, the addition of the enzyme eliminated the bactericidal effect caused by the polyphenols. In the research conducted by Poli et al. [46], five tested honeys, characterized by high antioxidant capacity: 2.76–8.6 ORAC ($\mu\text{mol/TE/g}$ of honey) and high content of H_2O_2 (23–54 $\mu\text{mol/l}$), have antibacterial properties (plasmid DNA degradation) against the bacteria *Pseudomonas aeruginosa*. According to research by Taleb et al. [40], hydrogen peroxide was also produced in media with the addition of polyphenol-rich date syrup (605 mg polyphenols/100 g of product), such as tannins, flavonoids, flavonols, anthocyanins, carotenoids. Thus, it has been proven in the research that with the increase in the concentration of date syrup (and thus polyphenols) in the medium, the concentration of H_2O_2 also increases. The hydrogen peroxide formed in the medium inhibited the multiplication of *Escherichia coli* and *Staphylococcus aureus*.

The self-oxidation of polyphenols with the simultaneous synthesis of hydrogen peroxide is therefore considered to be a bactericidal process with a generally beneficial effect on human health [47, 48].

Free radicals resulting from the auto-oxidation of polyphenols can be detected using the spin resonance technique. In studies conducted by Grzesik et al. [31], it was observed that as a result of PG and EGCG self-oxidation, hemiquinone radicals are formed. Thus, the use of the spin resonance technique made it possible to observe that ascorbic acid (one of the main components of lemon juice) significantly reduces the production of H_2O_2 in tea (acidification of the environment—inhibition of self-oxidation). The process of H_2O_2 production as a result of oxidation of antioxidant compounds has also been observed in in vivo processes. In a study by Lambert et al. [49], the micromolar synthesis of hydrogen peroxide occurs when the green tea solution is kept in the mouth. Hiramoto et al. [50] found clearly higher concentrations of H_2O_2 in the urine of coffee drinkers (urinary oxidation of coffee hydroxychromate). It is worth emphasizing, however, that the mechanism of H_2O_2 production with the use of polyphenols in the culture medium is still a poorly understood process. Often, in vitro studies do not match the in vivo processes [31].

Impact of lactic acid bacteria on polyphenol activity

The research conducted by Smith et al. [51] demonstrated the presence of several different responses of lactic acid bacteria cells to the presence of polyphenols in the environment. These bacteria are able to inhibit activity of proanthocyanidins by modification or degradation of these molecules. Sometimes, in response to polyphenolic substances, bacteria are able to dissociate the polyphenol–substrate complex. Bacteria inhabiting the human digestive system, including

Lactobacillus genus bacteria, are able to metabolize plant-derived polyphenols provided along with food. Through catabolic reactions, they modify polyphenol structures [52]. The metabolism of polyphenolic compounds affected by lactic acid bacteria significantly decreases the toxicity level of primary compounds. For example, the metabolized products of such acids as caffeic, *p*-muramic and protocatechuic acids demonstrate lower antimicrobial potential than the acids in their primary form. However, such factors as the method of polyphenolic compound degradation, the ability ferment them and the possibility of surviving in their presence are individual features of each lactic acid bacteria (LAB) species [53].

Polyphenols present in food have various forms, such as esters, polymers and glycosides. Thus, before they are absorbed in the intestines, these compounds must be hydrolysed so that they can play an active role in the body. This is possible due to the intestinal microbiota [3]. Some probiotic bacteria, such as *Lactobacillus plantarum* IFPL935, demonstrate high enzymatic activity directed at metabolizing polyphenols. They are capable of synthesizing galloyl-esterase, decarboxylase and benzyl alcohol dehydrogenase. Owing to their demonstrated enzymatic activity, *Lactobacillus plantarum* IHPL935 bacteria are able to conduct hydrolysis of polyphenols isolated from grape pips. As a result of their reactions, pyrogallol, catechol and gallic acids are generated [10].

Structural modifications of polyphenols caused by the presence of lactic acid bacteria are individual features of each higher organism (human or animal). Thus, the accessibility of certain compounds and their effects are changeable [54]. Lactic acid bacteria can also have a considerable influence on the polyphenolic profile, following the fermentation of juices. According to Kwaw et al. [55], mulberry juice fermented using LAB is characterized by a higher polyphenol content compared to a control sample (raw, unfermented juice). Over 1000 $\mu\text{g/ml}$ of polyphenol compounds can be isolated from raw mulberry juice. Among the secondary metabolites of mulberry juice, syringic acids (31.43% of flavonoids), cyanidin-3-*O*-rutinoside (51.11% of anthocyanins) and quercetin (39.62% of flavonols) are the most dominant. As a result of juice fermentation using LAB, it is possible to obtain much higher concentrations of polyphenols in a sample. *Lactobacillus paracasei*, *Lactobacillus plantarum* and *Lactobacillus acidophilus* are able to increase the total content of polyphenols by up to 1516, 1661 and 1644 mg/ml, respectively. Similar results were obtained by Pérez-Gregorio et al. [56]. This effect can be related to the ability of LAB to synthesize hydrolytic enzymes, thanks to which it is possible to conduct hydrolyses of complex phytochemical compounds to much simpler structures. However, it must be stressed that the adaptation of lactic acid bacteria to environments containing polyphenols is an individual feature.

Within the species, there are also significant differences in the level of hydrolytic enzyme synthesis. Higher concentrations of polyphenols in juice fermented by LAB may also result from polymer degradation, as a result of which complex compounds are transformed into a free form. Polymer degradation is conditioned by phenol oxidases, the synthesis of which depends on LAB [57]. Moreover, the production of lactic acid by LAB bacteria, causing a decrease in the environmental pH value as a result of its increased level, may act on polyphenols as a stabilizing agent. Additionally, polyphenol-rich fruit juice fermentation results in considerable enhancement of its anti-oxidative properties [55]. Undoubtedly, lactic acid bacteria are able to ferment polyphenolic compounds, which results in a direct decrease in the amount of these compounds in plant products. Sunflower flour is a food product characterized by a high content of phenolic acid compounds (up to 4% of the total weight). However, chlorogenic acid (5-*O*-caffeoylquinic acid), i.e. the ester of caffeic and quinic acids (23–33 g of acid/kg of dry sunflower mass), constitutes 70% of the content of all the polyphenolic compounds that can be isolated from sunflower seeds [58, 59]. Among *Lactobacillus* genus bacteria, species capable of phenolic acid metabolism, including chlorogenic, caffeic, *p*-carbamic and protocatechuic acids, were identified [60–62]. In certain cases, LAB also exert an impact on the anti-oxidation potential of polyphenols in their environment. For example, the research conducted by Rúa et al. [63] demonstrated that bacteria such as *Lactobacillus rhamnosus*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus paracasei* subsp. *paracasei* and *Lactococcus lactis* subsp. *cremoris*, cause synergistic effects as regards the antioxidative activity of polyphenols contained in melon juice.

Metabolism of polyphenols in the human digestive system

Understanding the processes of polyphenol metabolism in the human digestive system is extremely important when determining the mechanism of their action in the body. Studies on the concentration of polyphenols in the plasma and urine of mammals suggest that the large part of phenolic compounds contained in the food reaches the small intestine, where they are further metabolized by microbiota. Polyphenols, such as hydroxycinnamic acids, can reach the colon intact and are probably only then broken down by the bacterial microbiota. Simpler compounds resulting from the decomposition of complex polyphenols may have different biological properties. They can have positive effect on health, but also thanks to them modulation of the intestinal microbiota is possible (including bacteria of the genus *Lactobacillus*) [64].

Metabolism of polyphenols by *Lactobacillus* spp. bacteria

Among the intestinal microbiota, bacteria of the genus *Lactobacillus* are characterized by the highest ability to tolerate polyphenolic compounds in the growth environment [65].

Lactobacillus bacteria have many enzymatic abilities that allow them to carry out the transformations described in Table 1.

Phenols, such as hydroxycinnamic acids (caffeic acid, *p*-coumaric acid, ferulic acid), present in the nutrient matrix affect the growth of the biomass of *Lactobacillus* bacteria in various ways. First of all, they change the course of metabolic processes such as lactic fermentation. An example of a compound that affects the modulation of LAB microbiota is undoubtedly gallic acid. Low concentrations of gallic acid significantly stimulate the growth and metabolic activity of *Lactobacillus* bacteria. In the case of high concentrations of gallic acid (above 3 mM), the integrity of the bacterial cell walls is disrupted, resulting in a disturbed pH gradient. Thus, polyphenols can delay carbohydrate metabolism by lactic acid bacteria [69].

The metabolism and degradation of polyphenols by lactic acid bacteria can also provide additional benefits. The phenolic acid reduction process may be an intermediate element in the re-oxidation of the reduced NADH cofactor. Thus, this process provides an energy benefit through NAD⁺ regeneration. According to research conducted by Silva et al. [72], *Lactobacillus plantarum* and *Lactobacillus collinoides* were able to grow in anaerobic conditions in an environment without additional electron acceptors. As a result of the process of reducing 4-vinylphenol to 4-ethylphenol, they increased the availability of NAD⁺.

Reduction of phenolic acids by LAB can be much more beneficial in strictly heterofermentative species. Species that carry out heterofermentative metabolic processes are characterized by lower energy efficiency than bacteria capable of carrying out homofermentative metabolic processes. Research conducted by Filannino et al. [69] proved that heterofermentative bacteria of the genus *Lactobacillus* tolerate the presence of phenolic acids in the growth environment in various ways. The minimal value inhibiting the growth of *Lactobacillus* (MIC) bacteria is a strain feature. It also depends on the group of polyphenols used. The highest ability to tolerate polyphenols in the growth environment was characterized by the *Lactobacillus curvatus* PE5 strain, whose MIC in the case of caffeic, *p*-coumaric and ferulic acid exceeded 23.7 mM. Strains belonging to the species *Lactobacillus fermentum* and *Lactobacillus brevis* also had high tolerability (23.7 mM concentration) of *p*-coumaric acid and ferulic acid. Research conducted by Filannino et al. [69] proved that bacteria of the genus

Table 1 Examples of compounds metabolized by *Lactobacillus* species

Strain	Metabolized compound	Detected metabolites	References
<i>Lactobacillus hilgardii</i>	Gallic acid Catechin	Pyrogallol Catechol Protocatechuic acid <i>p</i> -Hydroxybenzoic acid <i>p</i> -Hydroxybenzaldehyde <i>p</i> -Hydroxybenzyl alcohol Acetovanillone Homovanillic acid	[66]
<i>Lactobacillus spp.</i>	Ferulic acid	Vanillin	[67]
<i>Lactobacillus brevis</i> <i>Lactobacillus collinoides</i> <i>Lactobacillus plantarum</i>	Vinylphenols	Ethylphenols	[68]
<i>Lactobacillus brevis</i> <i>Lactobacillus curvatus</i> <i>Lactobacillus mesenteroides</i> <i>Lactobacillus rossiae</i>	Caffeic acid <i>p</i> -Coumaric acid Ferulic acid	Vinylcatechol <i>p</i> -Vinylphenol Vinylguaiacol Dihydrocaffeic acid Phloretic acid Dihydroferulic acid Ethylcatechol Ethylphenol Ethylguaiacol	[60, 69]
<i>Lactobacillus kunkeei</i>	<i>p</i> -Coumaric acid Caffeic acid	<i>p</i> -Vinylphenolic acid Dihydrocaffeic acid	[70]
<i>Lactobacillus rossiae</i> <i>Lactobacillus fermentum</i>	Caffeic acid Sinapic acid Ferulic acid	Dihydrocaffeic acid Dihydrosinapic acid Dihydroferulic acid	[71]
<i>Lactobacillus hammesil</i> <i>Lactobacillus brevis</i>	Ferulic acid Caffeic acid	Vinylguaiacol Vinylcatechol	[71]
<i>Lactobacillus fermentum</i> <i>Lactobacillus rossiae</i> <i>Lactobacillus kunkeei</i>	Hydroxycinnamic acids	Phenylpropenoic acids	[71]

Lactobacillus grow relatively poorly in the environment in which the caffeic acid is found (MIC 13.6 mM).

According to research conducted by Gaur et al. [71] heterofermentative bacterial species of the genus *Lactobacillus* have a much higher ability to degrade hydroxycinnamic acids (using reductases) than homofermentative species. Thus, the degradation of hydroxycinnamic acids is one of the few known processes of polyphenol degradation by LAB. The ability to metabolize hydroxycinnamic acids also depends on the environment from which the strain was isolated. The most frequent reports in the literature describe the ability of bacteria of the species *Lactobacillus plantarum* to adapt and metabolize polyphenols. Nevertheless, among other plant isolates, this feature is also often attributed to the species *Lactobacillus collinoides* and *Lactobacillus buchneri*. Among animal isolates, the species *Lactobacillus delbrueckii* and *Lactobacillus salivarius* have the ability to metabolize polyphenols. It is worth remembering that the reduction of phenolic acids by heterofermentative species of lactic acid bacteria causes a

decrease in the amount of NADH which, at the same time, ensures higher energy efficiency of the cell.

Enzymatic transformation of polyphenols by *Lactobacillus* species

Among all species belonging to the genus *Lactobacillus*, in as many as 68 of them were genes found that are responsible for the ability to synthesize phenolic reductase, while genes responsible for the synthesis of phenolic decarboxylase are characteristic only of bacteria *Lactobacillus plantarum*. The most widespread species that have the ability to break down phenolic acid include *Lactobacillus rossiae*, *Lactobacillus reuteri*, *Lactobacillus fermentum* and *Lactobacillus plantarum*. As many as 34 bacterial species of the genus *Lactobacillus* have genes responsible for the synthesis of more than one type of reductase (e.g. vinylphenol reductase). Genes encoding as many as three different reductases have been found in species such as *Lactobacillus plantarum* and *Lactobacillus pentosus*. 19 bacterial species of the genus *Lactobacillus* have the ability to decarboxylate

hydroxycinnamic acids to vinyl derivatives, which in the next stages are transformed into ethyl derivatives [71].

Sometimes, despite the presence of genes encoding enzymes useful in the metabolism of polyphenols (e.g. feruloyl esterase) in the genome, bacteria of the genus *Lactobacillus* are unable to break them down. An example would be the fact that LABs are not able to metabolize methyl ferulate, methyl caffeine, methyl *p*-coumarinate or methyl sinapinate [73]. The ability to metabolize polyphenols is therefore a strain trait. Thus, in studies conducted by Gaur et al. [71], it has been proven that *Lactobacillus hammesil* and *Lactobacillus brevis* are able to metabolize ferulic and caffeic acid, while the species *Lactobacillus reuteri* and *Lactobacillus kunkeei* do not have this ability. *Lactobacillus plantarum* is believed to have the highest polyphenol metabolism capacity.

Lactobacillus plantarum is undoubtedly the best described bacterial species in terms of the enzymatic transformation of polyphenols. *Lactobacillus plantarum* has, among other things, the ability to produce benzyl alcohol dehydrogenase, which reversibly oxidizes some aromatic alcohols to aldehydes while reducing NAD⁺. *Lactobacillus plantarum* is also capable of hydrolyzing odorless, non-volatile glycosides with the formation of aglycones through the action of glycosidase. Phenolic acid decarboxylase allows *Lactobacillus plantarum* bacteria to break down *p*-coumaric acid, caffeic acid and ferulic acid. In addition, *Lactobacillus plantarum* bacteria are able to hydrolyse ester bonds in tannins and gallic acid esters due to their ability to produce tannin acyl hydrolase. Among other enzymes, the synthesis of which *Lactobacillus* bacteria are capable of, include esterases, reductases, and decarboxylases [74].

Examples of metabolic transformations using enzymes synthesized by *Lactobacillus plantarum* are presented in Table 2.

The ability of *Lactobacillus plantarum* to metabolize polyphenols may be due to the fact that this species is commonly found in products of plant origin. Plant fermentation requires *Lactobacillus plantarum* to have enzymatic capabilities that ensure the ability to ferment phenolic compounds. Thus, the use of *Lactobacillus plantarum* as a starter culture in the production of fermented foods carries some risk of organoleptic changes in the finished product. Due to the fact that these bacteria are capable of metabolizing hydroxycinnamic acids with the simultaneous release of vinyl and ethyl derivatives (which can react with anthocyanins and 3-deoxyanthocyanins to form pyrananthocyanins and 3-deoxyproanthocyanins), there may be changes in the aroma of fermented food. On the other hand, by releasing hydroxycinnamates, *Lactobacillus plantarum* helps to increase a product's health value. Hydroxycinnamates are compounds with antioxidant, anti-inflammatory and antimicrobial activity [71, 73]. *Lactobacillus plantarum*, as the only one in the genus *Lactobacillus*, also has the ability to synthesize the enzyme tannase. Owing to this, *Lactobacillus plantarum* is able to metabolize tannins (tannic acid) to gallic acid and glucose. In subsequent stages, bacteria convert gallic acid to pyrogallol [78]. Therefore, the enzymatic capabilities of bacteria of the genus *Lactobacillus* may be of particular importance in the selection of starter cultures in processes based on food fermentation. The new trend in functional food is the removal of antinutritional factors (ANF) from natural products, among which some polyphenols can be identified. Tannins that can be found in some foods are considered undesirable compounds (due to their ability to inhibit digestive enzymes). In studies conducted by Saez et al. [79] it was demonstrated that two strains of *Lactobacillus plantarum* had the ability to synthesize decarboxylases capable of breaking down tannins and gallic acid.

Table 2 Phyto compounds metabolized by *Lactobacillus plantarum*

<i>Lactobacillus plantarum</i>	Metabolized compound	Detected metabolites	References
	<i>p</i> -Coumaric acid	Floretic acid	[75]
	Tannic acid	Gallic acid	[74]
	Protectechic acid	Catechol	[76]
	Gallic tannin esters	Gallic acid	[65]
	Gallic acid	Pyrogallol	[65, 77]
	<i>p</i> -Coumaric acid caffeic acid ferulic acid	Vinyl derivatives (vinylphenol, vinylcatechol, vinylguaiacol)	[64, 77]
	Vinyl derivatives (vinylphenol, vinylcatechol, vinylguaiacol)	Ethyl derivatives (ethylphenol, ethylcatechol, ethylguaiacol)	[71, 77]
	Hydroxycinnamates (<i>p</i> -coumaric acid, <i>m</i> -coumaric acid, caffeic acid, ferulic acid)	Phloretic 3-(3-hydroxyphenyl) propionic acid dihydrocaffeic acid dihydroferulic acid	[71, 77]
	Sinapic acid	Dihydrosinapic acid	[71]

Prebiotic activity of polyphenols

Apart from their ability to limit the development of microbiota considered as pathogenic, some polyphenols (and their metabolites) are able to stimulate the growth of commensal bacteria populating the human intestinal system [80]. Some polyphenols are able to inhibit the multiplication of microbiota exhibiting a probiotic potential; in most cases, they demonstrate prebiotic characteristics. According to the research conducted by Attri, Goel [81], polyphenols derived from sea buckthorn, during 10-day supplementation, may increase the multiplication of lactic acid bacteria 1.18-fold. Despite the initial nearly 20% inhibition of bacteria multiplication, after a 48-h incubation period, lactic bacteria adapt to environmental conditions. The biomass increases its size up to approximately 10 logarithmic units (LU). A similar effect was also observed in tests conducted by Dolara et al. [82]. Feeding rats with red wine powder resulted in a considerable increase in the number of *Lactobacillus* genus bacteria in animal faeces. On the other hand, the tests conducted by Tabasco et al. [10] show that polyphenols (including catechin, epicatechin and flavan-3-ol), in concentrations of 0.25–1.0 mg/ml, effectively become growth stimulators for strains of LAB. More interestingly, when these polyphenols are used as individual compounds, they sometimes contribute to the inhibition of the growth of such bacteria as *Lactobacillus plantarum*, *Lactobacillus casei* and *Lactobacillus bulgaricus*.

Tests conducted on groups of mammals (rats, pigs and humans) and birds (chickens) proved that polyphenols isolated from grape pip extracts [83], blackcurrants [84], and wine [82] demonstrate a prebiotic potential in relation to *Lactobacillus* genus bacteria. Simultaneously, they contribute to inhibition of the multiplication of the *Enterobacteriaceae* family and *Bacteroides* and *Clostridium* genus bacteria. Their ability to demonstrate a prebiotic potential enables polyphenols to influence the modulation of intestinal microbiota [85].

Phenolic compounds (concentration: 10% v/v–2.9 mg/ml) contained in sunflower flour contribute significantly to enhancing the metabolic capabilities of lactic acid bacteria and producing significantly larger amounts of lactic acid. This results from the fact that polyphenols contained in sunflower seeds ensure the higher development potential of the following bacteria: *Bifidobacterium animalis* subsp. *lactis*, *Lactobacillus plantarum* and *Lactobacillus gasseri*. Phenolic acids from sunflower flour are an additional source of carbon [86] in this environment. Undoubtedly, another polyphenolic compound influencing the development of the LAB is chlorogenic acid. It must be stressed that metabolites generated during interactions between polyphenols and intestinal microbiota may be a factor conditioning its multiplication. This effect can be bidirectional, i.e. they can

be either activators or inhibitors of intestinal microbiota growth. Not all lactic acid bacteria are able to develop in the presence of polyphenolic compounds. According to the research conducted by Stead [87], hydroxycinnamic, caffeic, coumaric and ferulic acids inhibit the development of *Lactobacillus brevis* bacteria, at a concentration of 0.5 mg/ml. However, the tests conducted by Parkar et al. [88] proved that chlorogenic and caffeic acids, at the concentration of 0.25 mg/ml, inhibit the growth of *Lactobacillus rhamnosus* bacteria. Generally, lactic acid bacteria demonstrate much higher resistance to polyphenols, in comparison to pathogenic microbiota. The decrease in the number of lactic acid bacteria (*Lactobacillus plantarum*, *Lactobacillus gasseri* and *Pediococcus pentosaceus*), during a 24-h incubation period, only takes place after a 10–20 mg/ml concentration of polyphenols is administered. For example, a 24-h period of incubation of such pathogenic bacteria as *Escherichia coli*, *Staphylococcus aureus* and *Salmonella enterica* in the presence of chlorogenic acid, at 100 times lower concentration (0.1–0.2 mg/ml), results in significant inhibition of their growth [88, 89]. Polyphenol-rich melon juice (at pH 6.7) demonstrates bactericidal properties in relation to the probiotic strain of *Lactobacillus rhamnosus* only at a concentration of 5 mg/ml. On the other hand, an addition of melon juice at a concentration of 10 mg/ml to a cultivation base does not inhibit multiplication of such lactic acid bacteria as *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Lactobacillus paracasei* subsp. *paracasei* and *Lactococcus lactis* subsp. *cremoris* [63].

The positive effect of the prebiotic potential of compounds resulting from polyphenol metabolism results in the fact that the level of multiplication of probiotic intestinal microbiota is significantly higher. This, in turn, ensures better protection against stomach and intestinal disorders and additional protection against pathogenic microorganisms [90, 91]. In research on polyphenols present in pomace extracts from pseudo-fruit *Rosa rugosa* Thunb., Piekarska-Radzic et al. [92] proved that depending on the concentration used, the extracts can act as a factor stimulating the growth of *Lactobacillus* bacteria. Extracts from *Rosa rugosa* Thunb. (rich in polyphenols such as ellagitannins, free ellagic acid, flavonols, procyanidins and free catechins) are characterized by a total content of polyphenols at the level of 8.8–33.2 g/100 g dry matter. Thus, the addition of extracts with polyphenols at 0.156 mg/ml concentration to the bacteria culture of the genus *Lactobacillus* is the main factor determining of biomass growth. In case of the *Lactobacillus acidophilus* ŁOCK 0928 strain, the water–ethanol extract polyphenols increased biomass growth by almost 15% compared to the control culture. With *Lactobacillus brevis* ŁOCK 0944 bacteria, a higher degree of biomass multiplication (7–10%) was observed in cultures with the addition of purified water–ethanol extract

and crude water–acetone polyphenols. The authors also presented the results of studies showing that polyphenols at a concentration of 0.156 mg/ml (purified water–ethanol extract) added to the *Lactobacillus casei* LOCK 0979 are a factor stimulating biomass growth (by about 16% compared to the control culture). Thus, Piekarska-Radzik et al. [92], proved that bacteria of the genus *Lactobacillus* have the ability to tolerate polyphenols in the environment. They also emphasize the prebiotic potential of polyphenols contained in pseudo-fruit of *Rosa rugosa* Thunb.

In studies conducted by Filannino et al. [70], 54 strains of bacteria from the genus *Lactobacillus* constituting the intestinal microbiota of honeybee (*Apis mellifera* L.) were isolated—52 strains from the species *Lactobacillus kunkeei*, and one strain each of *Lactobacillus plantarum* and *Lactobacillus fermentum*. Further analysis showed that only 11 strains among the *Lactobacillus kunkeei* species could be classified as FLAB (fructophilic lactic acid bacteria). Interestingly, fructophilic lactation bacteria placed in the digestive tract of a honeybee was able to grow in an environment containing polyphenols such as *p*-coumaric acid, caffeic acid, gallic acid and syringic acid. The minimum value inhibiting bacterial growth was 22.7 mmol/L. The addition of *Lactobacillus kunkeei* to the above-mentioned polyphenols in the 1 mmol/L culture to the culture did not significantly affect the biomass increase. Nevertheless, Filannino et al. [70] observed that FLAB has the ability to consume secondary metabolites of plants. *Lactobacillus kunkeei* degraded *p*-coumaric acid in

57–78%, caffeic acid 43–50%, syringic acid 40–53% and gallic acid 42–51%.

In the literature, there is also other evidence confirming the prebiotic properties of plant extracts rich in polyphenols. Examples of plants characterized by a high content of polyphenolic compounds that favourably affect the growth of *Lactobacillus* bacteria are presented in Table 3.

Sometimes, incubation of *Lactobacillus* bacteria (especially those with probiotic potential) can change the specific strain characteristics. Among these, the production of short-chain fatty acids (SCFA) can be distinguished. Zhang et al. [98] proved that polyphenols abundantly found in oolong tea (epigallocatechin gallate, galactocatechin gallate) not only significantly affected the growth of *Lactobacillus* bacteria. The addition to the tea-based extract culture resulted in SCFA synthesis at a much higher level, particularly formic, acetic, propionic and butyric acid. Interestingly, during 24-h incubation, the synthesis of lactic acid (which is the base for the production of other SCFAs) by *Lactobacillus* spp. in the control sample occurred much more slowly than in cultures with the addition of polyphenols.

Influence of polyphenols on *Lactobacillus* spp. gene regulation

The interaction between polyphenols supplied with food and the microbiota inhabiting the human digestive tract is not limited to changes in the level of biomass multiplication. Phenolic compounds are able to cause changes in

Table 3 Examples of compounds with prebiotic activity towards *Lactobacillus* species

Source of polyphenols	Dominant polyphenol group	Analysed organisms	References
Hummingbird tree (<i>Sesbania grandiflora</i> L.)	Routine	<i>Lactobacillus acidophilus</i>	[93]
Grape seed	Gallic acid (+)-catechin (-)-epicatechin	<i>Lactobacillus</i> spp.	[94]
Sesame honey (<i>Sesamum indicum</i> L.)	Apigenin quercetin routine ferulic acid sesamin	<i>Lactobacillus</i> spp.	[95]
Starkrimson pears	Gallic acid <i>p</i> -coumaric acid quercetin derivatives catechin chlorogenic acid	<i>Lactobacillus helveticus</i>	[96]
Bartlett pears	Gallic acid <i>p</i> -coumaric acid quercetin derivatives caffeic acid	<i>Lactobacillus helveticus</i>	[96]
Elderberry fruits (<i>Sambucus nigra</i> L.)	Anthocyanins (expressed as cyanidin-3-glucosides)	<i>Lactobacillus rhamnosus</i>	[97]
Italian red grapes (<i>Vitis vinifera</i> L.)	Anthocyanins	<i>Lactobacillus rhamnosus</i>	[97]

gene expression in bacteria belonging to the *Lactobacillus* species.

In studies on the interaction between polyphenols and intestinal microbiota by Reverón et al. [64], a strain of *Lactobacillus plantarum* was used. After a 10-min incubation of bacteria together with *p*-coumaric acid at a concentration of 1.5 mM, significant differences in gene expression (9%) were observed. 280 transcripts changed (increased expression in 144 genes; reduced expression in 136 genes). The largest group of genes whose expression was changed was responsible for amino acid transport and metabolism, translation and cell wall and membrane synthesis. The shock caused by the presence of polyphenols in the environment caused that *Lactobacillus plantarum* expressed the genes coding proteases or heat shock proteins at a higher level. In the case of the *Lactobacillus plantarum* species, similar results were achieved in studies conducted by Esteban-Torres et al. [73]. Under the influence of olive oil rich in polyphenols such as hydroxytyrosol (9.31 µg/g) and *p*-coumaric acid (0.14 µg/g), 230 transcripts changed (increased expression in 123 genes; reduced expression in 107 genes). In turn, research by Santamaria et al. [99] regarding changes in gene expression in the genome of *Lactobacillus plantarum* under the influence of oleuropeins (concentration 15 mM) proved that after a 10-min incubation in the bacterial genome there was a change in the expression of as many as 358 genes (increased expression of 155 genes; reduced expression of 203 genes).

There is evidence in the literature that many polyphenolic compounds have the ability to alter the gene expression of *Lactobacillus* bacteria. Changes were observed after the addition of, among others, polyphenols such as jasmonic acid, jasmonate, gallic acid, salicylic acid and resveratrol to culture media [99].

The addition of polyphenols can contribute to changes in the expression of genes responsible for the synthesis of specific enzymes, genes encoding proteins (including those responsible for transport), and the induction of many metabolic processes [64, 73, 77, 99, 100].

Polyphenols often found in food (such as hydroxycinnamic acids) in bacteria of the genus *Lactobacillus* can cause increased expression of the genes responsible for the transport of purines, oligopeptides (ATP-dependent transport), branched chain amino acids, methionine, Na⁺ ions (indirect effect on homeostasis regulation), dihydroxyacetone, saccharides (mannose, mannitol, cellobiose, fructose). At the same time, they contribute to reduced transport of pyrimidines, NH₄⁺ ions, *N*-acyl-glucosamine or electrons (disorders in respiratory metabolism) [64, 73, 77, 99, 100].

Polyphenols are also responsible for increased expression of *Lactobacillus* spp. genes responsible for biosynthesis of chorismate, asparagine, methionine, cell wall surface proteins (increased synthesis of peptidoglycan; strengthening the cell wall; increase survival in the gastrointestinal tract),

oxidative shock proteins (antioxidant oxidation protein), proteins involved in cell proliferation, polysaccharides (extracellular), D-lactate (the basic component of peptidoglycan); protein acetylation, lactate racemization, transpeptidation; tRNA accumulation. At the same time, under the influence of polyphenols, the expression of genes responsible for biosynthesis is reduced: purines, capsular polysaccharides, serine, glutamine, cysteine, proteins constituting the autoaggregation factor, proteins involved in the FAB pathway, fatty acids, transcription factor constituting a global repressor of nitrogen metabolism; cell assimilation of nitrogen (altered production of glutamine and ammonium ions) [64, 73, 77, 99, 100].

Polyphenols also affect the expression of genes responsible for the synthesis of many specific enzymes. As a result of the action of polyphenols, there is an increased expression of genes responsible for the synthesis of enzymes such as transketolase, phosphoglycerate mutase, phosphoketolase, glutathione reductase, methionine sulfoxide reductase, oxidoreductase [NAD-dependent (P)], quinoxone oxidoreductase, quinoxone oxidase pyruvate metabolism), glycosidase transferase, acetyl CoA synthase, glycerol phosphate dehydrogenase, glyceryl kinase, D-lactate dehydrogenase, peptidoglycan hydrolase), glucosamine-6-phosphate deaminase, glucosamine-6-phosphate isomerase. On the other hand, the expression of genes responsible for the synthesis of phosphoglycerate dehydrogenase, nitrate reductase, peptide glycan hydrolase, *N*-glucosamine phosphotransferase, galactosamine phosphotransferase, acetate kinase, methionyl-tRNA formyltransferase, and cell wall transglycosidase is reduced [64, 73, 77, 99, 100].

Summary

The trend of combining both probiotic bacteria and polyphenols in food has caused that more products on the food market are appearing in the “functional food” category. Attempts to identify mechanisms connecting polyphenols and probiotic bacterial species of the *Lactobacillus* genus have led to the conclusion that the interaction between both groups can significantly affect the survival time of the bacteria in a product. Such factors as the common presence of lactic acid bacteria in the environment and the high content of polyphenols in plant-derived products have facilitated the development of unique interactions between them. From the point of view of higher organisms, the activity of intestinal flora, in particular *Lactobacillus* genus bacteria, results in an increase in the antioxidation potential of polyphenols. Due to the specificity of the metabolism of plant compounds contained in food, lactic acid bacteria are able to assist the host organism to assimilate compounds demonstrating antioxidative activity, frequently gaining access to substances

demonstrating a prebiotic potential. Moreover, in the presence of polyphenols, lactic acid bacteria ensure higher concentrations of lactic acid, which simultaneously stabilizes phytochemicals. A combination of correctly selected polyphenols and LAB bacteria in the food matrix makes it possible to produce food demonstrating a high functional potential. Such research conforms to the current worldwide policy of searching for food that demonstrates high nutritional potential and ensures microbiological safety.

It is worth emphasizing how important it is to learn about the mechanisms linking polyphenols with microorganisms. The interactions of compounds of plant origin present in food, with the intestinal microbiota are extremely important. Changing gene expression in both microorganisms with prebiotic potential and pathogenic (food contaminating) microbiota directly affects human health. By adding appropriately selected polyphenols to food, it is possible to influence gene expression responsible for virulence (i.e. *Escherichia coli*), protecting potential consumers against infections. Thus, it is worth noting that it is possible to design modern food protection systems against undesirable microbiota that contaminate food.

Polyphenols delivered with the diet to the human gastrointestinal tract may behave either as antioxidants or pro-oxidants. By appropriate regulation of the pH (especially in food products), it is possible to create a favourable pro-oxidative environment in which polyphenols turn out to be bactericidal against pathogenic bacteria. On the other hand, from the point of view of bacteria belonging to the genus *Lactobacillus*, hydrogen peroxide generated in the process of self-oxidation of polyphenols would introduce a mild degree of oxidative stress (which, in consequence, may lead to increased expression of genes encoding catalase, superoxide dismutase—higher survivability). Interestingly, bacteria of the genus *Lactobacillus* also have the ability to produce H₂O₂ (a by-product of the process of aerobic cellular respiration or oxidation of hydrocarbons), which limits the development of undesirable intestinal microbiota and promotes the regeneration of the intestinal epithelium. The combination of polyphenols and *Lactobacillus* spp. bacteria may therefore have a significant impact on maintaining homeostasis in the human gastrointestinal tract.

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Compliance with ethical standards

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