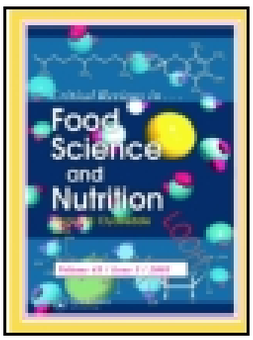

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Potential interactions among phenolic compounds and probiotics for mutual boosting of their health-promoting properties and food functionalities – A review

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ABSTRACT

Several foods are rich sources of phenolic compounds (PC) and their beneficial effects on human health may be increased through the action of probiotics. Additionally, probiotics may use PC as substrates, increasing their survival and functionality. This review presents available studies on the effects of PC on probiotics, including their physiological functionalities, interactions and capability of surviving during exposure to gastrointestinal conditions and when incorporated into food matrices. Studies have shown that PC can improve the adhesion capacity and survival of probiotics during exposure to conditions that mimic the gastrointestinal tract. There is strong evidence that PC can modulate the composition of the gut microbiota in hosts, improving a variety of biochemical markers and risk factors for chronic diseases. Available literature also indicates that metabolites of PC formed by intestinal microorganisms, including probiotics, exert a variety of benefits on host health. These metabolites are typically more active than parental dietary PC. The presence of PC commonly enhances probiotic survival in different foods. Finally, further clinical studies need to be developed to confirm *in vitro* and experimental findings concerning the beneficial interactions among different PC and probiotics.

KEYWORDS

Phenolics; probiotic; health-promoting effects; food functionality

1. Introduction

Approximately 8000 different compounds naturally occurring in plants are phenolics, which are mostly found in bound forms (e.g., as glycosides or esters), with a minor part in free form (Arceusz et al. 2013; Silva et al. 2016). These compounds are largely distributed in fruits, vegetables, herbs, seeds, cereals, honey and beverages (e.g., coffee, tea and wine) (Hossen et al. 2017). Phenol-Explorer, a database of polyphenol contents in foods, classified 501 polyphenols into six different classes (flavonoids, lignans, non-phenolic metabolites, other polyphenols, phenolic acids and stilbenes) and 31 sub-classes based on their chemical structures (Neveu et al. 2010).

Phenolic compounds are derived from universally present precursors (e.g., acetyl coenzyme A, amino acids and shikimate) with an aromatic ring with varying hydroxyl-substitutions as a primary structural characteristic (Harnly et al. 2007; Silva et al. 2016). The flavonoid-type phenolics have a primary structure of two benzene rings (A and B) connected through a heterogeneous pyrone C ring. Nonflavonoid-type phenolics include a group of compounds varying from the simplest benzoic acids to more complex stilbenes, lignans, gallotannins, hydrolysable tannins and ellagitannins (Ozdal et al. 2016). Despite having the same basic skeleton and structural characteristics, the position and number of hydroxyl groups in phenolic compound molecules have a primary influence on their biological and functional properties (Granato et al. 2016). The chemical structure of different groups of phenolic compounds is shown in Figure 1.

The health benefits of phenolic compounds are typically related to their antioxidant and anti-inflammatory properties. These characteristics are associated with the ability of phenolic compounds to donate hydrogen or electrons to free radicals, which stabilizes cell membranes, offers protection against oxidative processes and inhibit different pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNFa-α) and interleukins (e.g., IL-6 and IL-8) (Essafi-Benkhadir et al. 2012; Jiang et al. 2013; Li et al. 2014; Espinosa et al. 2015; Farhadi et al. 2016). The available literature has shown that phenolic compounds may exert health benefits at a local level when they act directly during passage through the gastrointestinal tract and at a systemic level after they are absorbed, which includes anti-cancer, antioxidant and anti-inflammatory properties; they also prevent chronic pathologies, such as diabetes, obesity, cardiovascular and neurodegenerative diseases (Farhadi et al. 2016; Zhang and Tsao 2016; Cueva et al. 2017).

To exert these beneficial effects, phenolic compounds must be absorbed in the intestinal tract and be bioavailable in the circulatory system. When they are not absorbed in the small intestine, phenolic compounds reach the colon, where they may undergo extensive biotransformation by the resident microbiota, which may improve their absorption and bioavailability. Probiotics have shown capable of causing biotransformation of phenolic compounds through the action of different glycosyl-hydrolases via the release of aglycones from glycol-conjugated phenolic compounds (Rossi et al. 2013; Pereira-Caro et al.

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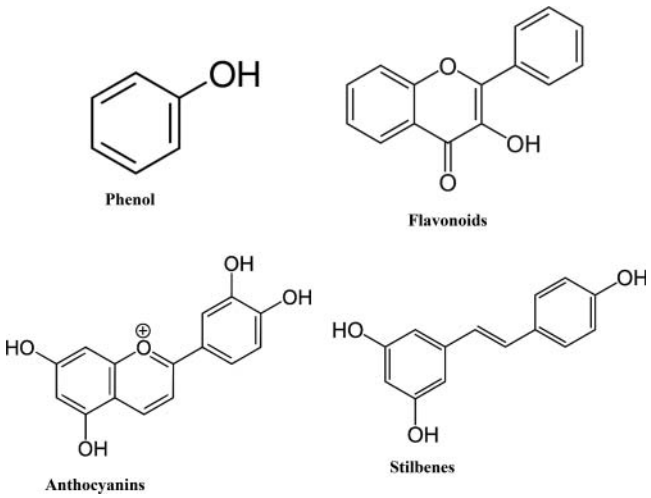

Figure 1. Chemical structures of different groups of phenolic compounds.

2015). Probiotics are defined as "live microbes, which when administered in adequate amounts, confer health benefits to the host". Additionally, these microorganisms must meet safety criteria for consumption, present beneficial physiological functionalities, and be able to survive during gastrointestinal passage and food processing and storage (Saarela et al. 2000; FAO/WHO 2006). Lactic acid bacteria and bifidobacteria are the most common types of microorganisms used as probiotics, although other bacteria (e.g., Bacillus and Escherichia coli) and certain yeasts (e.g., *Saccharomyces*) are also used. Biological effects of probiotics have been strain specific, and the success or failure of one strain for a specific health claim should not be extrapolated to another strain (Fijan et al. 2014).

Recent studies have shown that phenolic compounds may mostly modulate the composition of gut microbial communities through the inhibition of pathogenic bacteria and stimulation of beneficial bacteria. In the latter, phenolic compounds may exert a prebiotic function and increase the population of beneficial bacteria, including probiotics, suggesting a mutual relationship between phenolic compounds and probiotics (Ozdal et al. 2016; Llano et al. 2017; Succi et al. 2017). This review provides an update and discusses available literature concerning the effects of phenolic compounds on probiotics, including their physiological functionalities, interactions and capability of surviving during exposure to gastrointestinal conditions and in food matrices. Particularly, this review focuses on the possible interactions among phenolic compounds and probiotics as a strategy to boost their health-promoting properties and functionalities when incorporated or naturally present into foods.

2. Effects of microbial metabolism on bioavailability of phenolic compounds

The benefits of phenolic compounds ingestion on human health depend primarily on their absorption, metabolism and bioavailability. Many phenolic compounds occur in food as esters, glycoconjugates or polymers, which are not directly bioavailable (Rossi et al. 2013). There are estimates that as little as 5–10% of total ingested phenolic compounds can be absorbed in the small intestine, whereas 90–95% reach the colon because of insufficient gastric residence time, low permeability or solubility in the intestine (Pereira-Caro et al. 2015; Llano et al. 2016; Cueva et al. 2017).

The phenolic compounds non-absorbed in the small intestine reach the colon, where they are metabolized through the action of microorganisms that form the gut microbiota. The ability of bacteria to metabolize different substrates is species-specific or strain-specific and depends on their ability to produce different enzymes, such as β-glucuronidases, sulfatases and glucosidases (Possemiers et al. 2011). There is large diversity in the bacterial species that form the gut microbiota in different individuals. Bacterial diversity has been associated with differences in the types of metabolites formed during the metabolism of phenolic compounds by the gut microbiota, which could be related in part to the variable effects of phenolic compounds ingestion in different individuals (Duda-Chodak et al. 2015).

The specific structural characteristics of phenolic compounds seem to influence their microbial biotransformation. The metabolism of phenolic compounds by the gut microbiota commonly involves A- and C-ring cleavage, dioxygenase-mediated C-ring cleavage, dehydroxylation and alkene hydrogenation (Stevens and Maier 2016). Studies on the metabolism of polyphenols by intestinal microorganisms have demonstrated that after colonic metabolism, phenolic compound-derived metabolites are absorbed and have a residence time of 24 – 48 h in the bloodstream before they are excreted in urine (Szwajgier and Jakubczyk 2010; Flores et al. 2015; Vetrani et al. 2016). The results of *in vitro* studies and clinical trials using phenolic compound-rich foods and beverages have indicated that the carbon backbone of phenolic compounds is partly metabolized through colonic microbial conversion, followed by an additional post colonic hepatic conversion (Vetrani et al. 2016). These results suggest that the gut microbiota exerts a key role in the bioavailability of phenolic compounds and their derived metabolites.

In the following paragraphs of this section, evidence on the microbial metabolism of the main classes of phenolic compounds is presented.

Anthocyanins: These compounds form one of the most widespread families of natural pigments of plants and are responsible for the red, purple and blue colours of flower petals, vegetables, berries and other fruit (Fernandes et al. 2014; Stevens and Maier 2016). The gut microbiota was observed to cause the deglycosylation and degradation of six anthocyanins, leading to the production of three different aglycones with mono or di-β-d-glycosidic bonds. All anthocyanidin glycosides may be hydrolysed by the gut microbiota within 2 h. The hydrolysis time period seemed to be dependent on the sugar moiety in anthocyanin molecules. These findings confirm the hydrolytic activity exerted by the intestinal microbiota to break glycosidic bonds (Keppler and Humpf 2005). Anthocyanins are hydrolysed to form their corresponding anthocyanidins, which are transformed by the gut microbiota into protocatechuic acid and acetic acid (Cheng et al. 2016; Stevens and Maier 2016).

Flavonols: These substances contain a 3-hydroxyflavone base (3-hydroxy-2-phenylchromen-4-one) and a planar ring. Quercetin is the most representative flavonol compound and is

naturally found in onion, broccoli, tea, apples, berries and red wine. Flavonols are extensively hydrolysed into their metabolite-derivative products by the gut microbiota at the A and B rings as a result of C-ring cleavage. This cleavage causes the formation of 2-(3,4-dihydroxyphenyl) acetic acid, 2-(3-hydroxyphenyl) acetic acid and 3,4-dihydroxybenzoic acid from the B ring, whereas phloroglucinol, 3-(3,4-dihydroxyphenyl) propionic acid and 3-(3-hydroxyphenyl) propionic acid are formed from the A ring. These metabolites enter the catabolic route of phenyl and benzoic acids to generate protocatechuic acid and 2-(3,4-dihydroxy)-phenylacetic acid as the major metabolites (Peng et al. 2014; Ozdal et al. 2016; Stevens and Maier 2016).

Stilbenes: Resveratrol is the largest representative of the stilbenes group, which is present in higher amounts in red grapes, red wine, cranberries, strawberries and peanuts. Studies on stilbene microbial metabolism are still scarce. A study demonstrated that the main resveratrol microbial metabolites are dihydroresveratrol and *m*-deoxy metabolites and that two other trans-resveratrol metabolites, namely, 3,4-dihydroxy-trans-stilbene and 3,4-dihydroxybibenzyl (lunularin), may be produced by selected faecal bacterial strains (Bode et al. 2013).

Bacterial phenolic compound metabolites may be absorbed in the colon and further metabolized in the liver by phase II enzyme glutathione S-transferase into conjugated metabolites (glucuronides and sulphates), which can be distributed to the tissues, come back to the intestine or be excreted in urine (Cueva et al. 2017).

3. *In vitro* effects of phenolic compounds on probiotic adhesion, growth and survival

Some studies have shown the effects that phenolic compounds can exert on the adhesion, growth and survival of probiotics. Current studies assessing the *in vitro* effects of phenolic compounds or phenolic compound-rich source extracts on the adhesion, growth or survival of probiotics are summarized in Table 1. The information presented in this table gives an overview of the tested phenolic compound or extract, monitored parameters and main effects on tested probiotics. Cellular adhesion is an important characteristic of probiotics, promoting gut colonization, contact between bacterial cell membranes, interaction with intestinal surfaces (Duary et al. 2011) and enhanced antagonistic activity against pathogens (Sengupta et al. 2013). Phenolic compounds seem to influence bacterial adhesion because the presence of hydroxyl groups in the molecules of the former, which enable the occurrence of protein-protein interactions (Bustos et al. 2012). Protein-like components are key factors in the adhesion of bacteria to intestinal mucin and/or epithelial cells (Vélez et al. 2007; Izquierdo et al. 2009).

Apple peel and pulp ethanolic extracts were evaluated considering their influence on the adhesion of *Lactobacillus gasseri* R and *Lactobacillus casei* FMP to intestinal epithelial Caco-2 and HT29-MTX cell lines. Apple pulp extracts decreased the adhesion of *L. gasseri* R and *L. casei* FMP to epithelial cell lines. In contrast, apple peel extract (richer in polyphenols) increased the adhesion properties of these strains. This study found quercetin to be the most active polyphenol, increasing adhesion by 95% in *L. gasseri* R (Volstatova et al. 2017). These findings suggested that phenolic compounds, particularly quercetin, may enhance adhesion and colonization of intestinal mucosa by the tested probiotic strains.

Lactobacillus acidophilus ATCC 1643 exhibited higher adhesion to intestinal cells in the presence of aqueous apple peel extract in comparison to the presence of ethanolic extract or the purified phenolic compounds rutin, epicatechin, phlorizin, cholorogenic acid, quercetin and p-coumaric acid. The different effects caused by aqueous and ethanolic extracts were associated with the method used to prepare these materials. The co-precipitation of polyphenols due to their interaction with apple cell wall components (e.g., proteins) could cause the solubility of apple polyphenols in polar (ethanolic) extract, causing decreased availability of these compounds to act on probiotic cells (Shinde et al. 2015).

Different flavan-3-ols inhibited the adhesion of *L. acidophilus* LA-05 and *Lactobacillus plantarum* IFPL379, except for epigallocatechin gallate, which increased the adhesion of *L. acidophilus* LA-05 to Caco-2 cells. Procyanidins B1 and B2 markedly increased the adhesion of *L. casei* LC115 to HT-29 cells, whereas epigallocatechin increased the adhesion of *L. casei* LC115 to Caco-2 cells (Bustos et al. 2012). Selective enhancing effects of naringenin, phloridzin and rutin on bacterial adhesion were observed. Naringenin and rutin increased the adherence of *L. rhamnosus* to Caco-2 cells, whereas naringenin and phloridzin decreased the adherence of the pathogen *Salmonella* Typhimurium to these cells (Parkar et al. 2008).

The combined use of wine polyphenols (+)-catechin and 3,4-dihydroxypheylacetic acid and *Lactobacillus* strains decreased the adhesion of *Escherichia coli* CIAL-153 to Caco-2 cells. These findings suggested that the tested polyphenols increased the ability of the *Lactobacillus* strains to adhere to Caco-2 cells, limiting additional *E. coli* adherence to the latter (Llano et al. 2017). Anthocyanin-rich blackcurrant juices enhanced the *in vitro* growth and adhesion properties of *L. rhamnosus* 299, in addition to inhibiting the growth and adhesion properties of *Salmonella* Typhimurium 450 (Parkar et al. 2014). The combination of native olive phenolic compounds, namely oleuropein and hydroxytyrosol, at the recommended levels of a daily ingestion dose of olives and probiotics showed enhancing effects on biofilm formation and adhesion capacity in *L. plantarum* 33 (Peres et al. 2015). The increased adhesion capacity of probiotics may reduce the incidence of gastrointestinal infections due to competitive exclusion with pathogens for host epithelial cell binding sites.

The improvement of bacterial adhesion capacity by phenolic compounds seems to depend on the number of multiple hydroxyl groups in phenolic compound molecules, which enable the occurrence of protein-protein interactions (Bustos et al. 2012; Shinde et al. 2015; Llano et al. al., 2017; Volstatova et al. 2017). Although previous studies have shown that phenolic compounds may increase the adhesion properties of probiotics, the mechanisms underlying these inductive effects still need to be clarified.

Additionally, the reduction in pathogen adhesion is a promising approach to prevent and control intestinal microbial infections. Biofilm formation is typically referred to as the initial step for adhesion and colonization by pathogenic bacteria (Chagnot et al. 2013; Lopes et al. 2017). Phenolic compounds

Table 1. Studies assessing the *in vitro* effects of phenolic compounds on the adhesion, growth or survival of probiotics.

References	Phenolic compound or extract	Probiotics	Main results
Hervert-Hernández et al. (2009)	Grape pomace phenolic extract	*L. acidophilus* CECT 903.	Stimulated bacterial growth.
Tabasco et al. (2011)	Flavan-3-ol enriched grape seed extract and the monomeric-rich and oligomeric-rich fractions	*L. plantarum, L. casei* and *L. bulgaricus*.	Probiotics reached maximum growth in media containing any of the three extracts. An inhibitory effect was observed depending on the tested extract concentration.
Sánchez-Patán et al. (2012)	Red wine extract	*Bifidobacterium* spp. (Sonda Bif164), *Lactobacillus / Enterococcus* spp. (Sonda Lab158).	No stimulatory effect on probiotic growth.
China et al. (2012)	Sesbania grandiflora flower polyphenol extracts	*L. acidophilus* MTCC 447.	Promoted bacterial growth.
Duda-Chodak (2012)	Naringenin, quercetin, naringin and rutin	*Lactobacillus* spp. (DSM 20059) and *Bifidobacterium catenulatum* (DSM 16992).	Naringenin and quercetin decreased the growth of evaluated intestinal bacteria. The glycosides narigin and rutin did not inhibit intestinal bacteria, and in some cases, they exerted stimulatory effects.
Bustos et al. (2012)	Flavan-3-ols	*L. acidophilus* LA-05 and *L. plantarum* IFPL379.	Inhibited probiotic adhesion.
Sourabh et al. (2013)	Green tea extract and flavan-3-ols	*Enterococcus faecium (*AdF1- GU396270; AdF2- GU396271; AdF3- GU396272 and AdF11- GU396279), *Bacillus coagulans* (AdF4- GU396273), *L. plantarum* (AdF5- GU396274; AdF6- GU396275 and AdF10- GU396278) and *L. fermentum* (AdF7- HQ677597; AdF8- GU396276 and AdF9- GU3962770).	Increased probiotic growth.
Parkar et al. (2014)	Anthocyanin-rich blackcurrant juices	*L. rhamnosus* 299.	Did not inhibit probiotic adhesion.
Lacey et al. (2014a)	Green tea polyphenols	*B. animalis* B94.	Glycosylated flavonoids allowed a higher probiotic survival rate.
Lacey et al. (2014b)	Green tea extracts	*L. paracasei* LAFTI-L26, *L. acidophilus* LAFTI-L10 and *B. animalis* B94.	Permitted the survival of the selected probiotic. The viability of *B. animalis* B94 was higher than that of *Lactobacillus* strains.
Das et al. (2015)	Sesame honey	*L. acidophilus* MTCC 447 and *B. bifidum* ATCC 700541.	Growth-promoting effects on probiotics.
Peres et al. (2015)	Oleuropein and hydroxytyrosol	*L. plantarum* 33.	Increased bacterial adhesion.
Shinde et al. (2015)	Aqueous apple peel extract; Ethanolic apple peel extract; Polyphenols (rutin, epicatechin, phlorizin, cholorogenic acid, quercetin and p-coumaric acid).	*L. acidophilus* ATCC 1643.	Increased bacterial adhesion. Highest adhesion inductive effects were induced by aqueous apple peel extract.
Kemsawasd et al. (2016)	Types of chocolate (white, milk and dark)	*L. casei* 01 and *L. acidophilus* LA-05.	Dark chocolate protected probiotic cells.
Klindt-Toldam et al. (2016)	Milk chocolate and 72% dark chocolate	*B. lactis* HN019 and *L. acidophilus* NCFM.	Protective effects on probiotics during passage through the gastrointestinal tract. The viability of *B. lactis* was higher than that of *L. acidophilus*.
Volstatova et al. (2017)	Quercetin, apple pulp extracts and apple peel extract	*L. gasseri R* and *L. casei* FMP.	Quercetin and apple peel extract increased probiotic adhesion. Apple pulp extracts decreased probiotic adhesion.
Campanella et al. (2017)	Grape marc	*L. plantarum* 12A, *L. plantarum* PU1, *L. paracasei* 14A and *Bifidobacterium breve* 15A.	Protective effect on probiotics during passage through the stomach conditions.
Coman et al. (2017)	Plum (skin), Italian red grape (skin) and elderberry (different parts) ethanolic extracts	*L. rhamnosus* IMC 501®, *L. paracasei* IMC 502® and *L. plantarum* IMC 509.	Growth-promoting effects on tested probiotics.
Succi et al. (2017)	Dark chocolate with high cocoa content (80%)	*L. paracasei* F19 and *L. rhamnosus* GG.	Protective effects on probiotics during exposure to simulated gastrointestinal conditions.
Silva et al. (2017)	Semi-sweet chocolate	*L. acidophilus* LA3 and *B. animalis* subsp. *lactis* BLC1.	Protective effect on probiotic when exposed to simulated gastric and intestinal fluids.
Valero-Cases et al. (2017)	Pomegranate juice fermented with LAB	*L. acidophilus* CECT 903, *L. plantarum* CECT 220, *B. longum subsp. infantis* CECT 4551 and *B. bifidum* CECT 870.	Growth-promoting effects on some of the tested probiotics.

have been shown to inhibit biofilm formation by pathogenic bacteria (Xu et al. 2014) and to interfere negatively with the survival of *Clostridium* spp., *Staphylococcus aureus, Salmonella* spp. and *E. coli* (Lee et al. 2006; Rodríguez-Pérez et al. 2016).

The effects of phenolic compounds on bacterial cell wall structure, bacterial toxin release and the ability to trap essential nutrients, which become inaccessible, especially to pathogenic bacteria, have also been studied (Kemperman et al. 2010; Cardona et al. 2013). The selective ability of probiotic strains to use phenolic compounds is a key factor favouring their growth (China et al. 2011; Hervert-Hernandez and Goni 2011). Researchers have consistently observed that phenolic-rich foods can improve the survival of probiotic strains during gastrointestinal digestion (Possemiers et al. 2010; Campanella et al. 2017; Silva et al. 2017a; Succi et al. 2017).

Grape marc has demonstrated protective effects on *L. plantarum* 12A, *L. plantarum* PU1, *L. paracasei* 14A and *Bifidobacterium breve* 15A through stomach passage. In the same study, lactic acid fermentation increased the antioxidant properties of grape marc on intestinal cells. These findings suggested mutual beneficial interactions among dietary phenolic compounds and probiotic strains. The content of phenolic compounds (e.g., gallic acid) was decreased in grape marc after fermentation, indicating that the tested probiotics were capable of metabolizing some phenolic compounds present in grape marc (Campanella et al. 2017). The influence of grape polyphenols on *L. acidophilus* CECT 903 growth was also studied. The growth of *L. acidophilus* CECT 903 was not affected by grape polyphenols or by caffeic acid, gallic acid, tannic acid, catechin, epicatechin and quercetin. Grape pomace phenolic extract and tannic acid remarkably stimulated the growth of *L. acidophilus* CECT 903 (Hervert-Hernández et al. 2009).

A study with red fruit (plum skin, Italian red grape skin and different parts of elderberry) ethanolic extracts characterized as polyphenol/anthocyanin-rich sources observed stimulatory effects of the tested extracts on the growth of *L. rhamnosus* IMC 501® and *L. paracasei* IMC 502® alone or in combination (SYMBIO®), as well as of *L. plantarum* IMC 509 in laboratory media. Additionally, the fruit extracts inhibited the growth of the pathogens *Bacillus cereus, E. coli, Listeria monocytogenes* and *S. aureus*. Combined formulation of plum skin extract or elderberry skin or seeds extracts and each of the four tested probiotics exhibited higher antioxidant activities than the extract alone, indicating the ability of the probiotics to enhance the antioxidant properties of the tested fruit extracts. Specifically, the highest stimulatory effects on the probiotics growth were exerted by fruit extracts rich in anthocyanins, suggesting that anthocyanins and/or their metabolites may modulate positively the intestinal bacterial population (Coman et al. 2017).

In contrast to studies that have observed stimulatory effects of grape polyphenols on probiotic bacteria, the use of red wine extract did not affect the growth of *Bifidobacterium* spp. (Sonda Bif164) and *Lactobacillus/Enterococcus* spp. (Sonda Lab158). These findings were associated with the possibility that the amount of flavan-3-ols in the tested red wine extract was not enough to exert stimulatory effects on the growth of the tested bacteria over a 48-h fermentation (Sánchez-Patán et al. 2012). A study using flavan-3-ol-enriched grape seed extract and oligomeric and monomeric fractions containing different polyphenol concentrations found a higher maximum growth rate for *L. plantarum, L. casei* and *L. bulgaricus* in media supplemented with the tested extract or fractions. However, exposure to 1 mg/mL grape seed extract caused slight inhibitory effects on all tested *Lactobacillus* strains. These impairing effects were attributed to the high amounts of gallate-derived compounds (e.g., (−)-epicatechin-3-O-gallate) in the tested grape seed extract (Tabasco et al. 2011).

Another study with the polyphenols present in green tea observed that glycosylated flavonoids stimulated the growth of *Bifidobacterium animalis* B94. The antioxidant activity of the tested polyphenols increased following incubation with *B. animalis* B94, which could indicate the use of catechins by this bacterium. Additionally, there was a direct relationship between the reduction of catechin content in the medium during the monitored incubation period and the increase in its antioxidant activity (Lacey et al. 2014a). Similarly, the presence of green tea extract and flavan-3-ols (−)- epigallocatechin-3-gallate, (−)- epigallocatechin, (−)- epicatechin-3-gallate, epicatechin and catechins stimulated the growth of different probiotics (*Enterococcus faecium* AdF1- GU396270, AdF2- GU396271, AdF3- GU396272 and AdF11- GU396279; *Bacillus coagulans* AdF4- GU396273, *L. plantarum* AdF5- GU396274, AdF6- GU396275 and AdF10- GU396278; and *L. fermentum* AdF7- HQ677597, AdF8- GU396276 and AdF9- GU3962770) (Sourabh et al. 2013). *B. animalis* LAFTI-B94 presented increased survival rates in different varieties of phenolic-rich green tea extracts in comparison to *L. paracasei* LAFTI-L26 and *L. acidophilus* LAFTI-L10. The tested probiotics were positive for β-glucosidase, β-galactosidase and α-rhamnosidase activities, which are enzymes involved in the degradation of phenolic compounds. The antioxidant and antihypertensive properties of epigallocatechin-3-gallate and rutin (used as a standard for green tea extract) increased after incubation with *B. animalis* B94 and was related to decreases in phenolic contents and the formation of more biologically active metabolites (Lacey et al. 2014b).

A polyphenol-rich extract from flowers of *Sesbania grandiflora* promoted the growth of *L. acidophilus* MTCC 447. The amount of rutin in the cultivation medium supplemented with the tested extract decreased after fermentation with *L. acidophilus* MTCC 447, indicating that this strain was capable of metabolizing rutin (China et al. 2012). Sesame honey, which presents a variety of phenolic compounds (e.g., apigenin, quercetin, myricetin, rutin and ferulic acid), also exhibited growth-promoting effects on *L. acidophilus* MTCC 447 and *Bifidobacterium bifidum* ATCC 700541 (Das et al. 2015). Some researchers have hypothesized that the stimulatory effects of phenolic compounds on probiotics could be associated with their effective antioxidant and oxygen-scavenging properties, which could modulate the oxidative stress generated from microbial metabolic activities, providing a favourable environment for probiotic growth and survival (China et al. 2012; Chaikham 2015).

Dark chocolate with high cocoa content (80%) and total phenolics has also showed protective effects on probiotic survival during exposure to simulated gastrointestinal conditions. Dark chocolate presented protective effects on freeze-dried *L. paracasei* F19 and *L. rhamnosus* GG during passage through

simulated gastrointestinal conditions (Succi et al. 2017). The viability of immobilized *L. casei* 01 and *L. acidophilus* LA5 in three different types of chocolate (white, milk and dark) were evaluated during exposure to simulated gastrointestinal conditions. All chocolate types exerted protective effects on the tested strains, but *L. casei* 01 presented higher survival rates than *L. acidophilus* LA5 during exposure to *in vitro* digestion. Dark chocolate presented higher protective effects on *L. casei* 01 and *L. acidophilus* LA-05 (Kemsawasd et al. 2016).

Similarly, other studies have observed the protective effects of semi-sweet chocolate on *L. acidophilus* LA3 and *B. lactis* BLC1 and milk chocolate on *B. lactis* HN019 and *L. acidophilus* NCFM when exposed to *in vitro* digestion (Klindt-Toldam et al. 2016; Silva et al. 2017a). These protective effects were associated with possible interactions of probiotics and chocolate ingredients (mostly phenolics and fat), which could decrease the damage in cells of probiotics imposed by their exposure to the harsh conditions found during gastrointestinal passage.

Some studies have suggested that excessive amounts of phenolic compounds reaching the colon could inhibit the growth of beneficial intestinal microorganisms that are normally involved in their bioconversion and consequent increased bioavailability. Naringenin and quercetin (aglycones) presented dose-dependent inhibitory effects on the growth of intestinal bacteria, including *Lactobacillus* sp. (DSM 20059) and *Bifidobacterium catenulatum* (DSM 16992). However, these inhibitory effects were not observed for the glycosides naringin and rutin. Flavonoid aglycones, but not their glycosides, have been suggested to inhibit the growth of some intestinal bacteria and their excessive consumption could cause non-beneficial changes in the composition and function of the gut microbiota (Duda-Chodak 2012).

4. Interactions among phenolic compounds and beneficial microorganisms in the host

A variety of beneficial effects of phenolic compounds on human health have been reported (Li et al. 2013; Igwe et al. 2017; Theodotou et al. 2017); however, available preclinical evidence has not yet reached a definitive consensus in clinical trials (Ganai and Farooqi 2015; Núñez-Sánchez et al. 2015, 2017). In part, this limitation may be due to the difficulty of attributing the observed beneficial effects to specific phenolic compounds, since most of the available studies have used foods containing different phenolic compounds or phenolic-rich extracts (Hossen et al. 2017). Furthermore, most of these studies have not considered the use of a realistic ingestion dose of phenolic compounds and plausible metabolic forms (e.g., conjugated, glucuronidated and sulphated) that can circulate in the bloodstream and reach tissues (González-Sarrías et al. 2017a; Manach et al. 2017). The large inter-individual variations in the effects of phenolic compounds observed in clinical trials have been partially related to differences in the intestinal microbiota composition and consequently to how microorganisms forming these communities metabolize these compounds (Espín et al. 2017).

In recent years, phenolic compounds have been placed on the same biological level as prebiotics for intestinal health (Marchesi et al. 2016). Beneficial actions of phenolic compounds, such as anti-inflammatory, antioxidant and antimicrobial activities, are believed to positively influence gut microbiota composition and function (Chuang and McIntosh 2011; Llano et al. 2017). Microorganisms forming the gut microbiota and phenolic compounds seems to exert a mutual interaction in which the phenolic compounds modulate the composition of the gut microbiota and intestinal microorganisms catabolize ingested phenolic compounds to release metabolites that are typically more active and better absorbed than parental dietary compounds (Espín et al. 2017; Llano et al. 2017).

Current studies on the effects of phenolic compounds or their extracts in hosts are summarized in Table 2. The information presented in this table provides an overview of the tested phenolic compound or extract, monitored parameters and main effects observed in the host.

4.1. Modulation of the intestinal microbiota by phenolic compounds

Preclinical studies have investigated the effects of phenolic compounds supplementation on modulation of the gut microbiota. Pigs fed a conventional cereal-based diet that received cocoa husk rich in B-type proanthocyanidins for 3 weeks had a decreased faecal population of the *Firmicutes* group and an increased population of the *Bacteroides-Prevotella* and *Faecalibacterium prausnitzii* group, indicating that the administration of cocoa husks may have a positive effect on gut microbial ecosystem balance (Magistrelli et al. 2016). The daily administration of cranberry and grape extracts, which are rich in type A and B proanthocyanidins, respectively, increased the population of the bacterium *Akkermansia muciniphila* in faecal samples from high-fat and high sugar fed mice (Anhê et al. 2015; Roopchand et al. 2015). A decreased faecal population of *A. muciniphila* has been associated with type 2 diabetes and obesity (Everard et al. 2013). These findings support the hypothesis that compounds derived from microbial transformation of phenolic compounds in the intestine may exert anti-diabetic properties or protect hosts from diet-induced obesity through a direct effect that depends on their intestinal absorption or through an indirect effect that depends on the positive modulation of the intestinal microbiota (Anhê et al. 2013).

Pomegranate peel extract supplementation increased the caecal population of *Bifidobacterium* spp. in mice fed a high-fat diet. Pomegranate peel extract did not modify body weight gain, glycaemia, glucose tolerance or inflammatory markers measured in the serum; however, it reduced the serum level of total and LDL cholesterol. Furthermore, pomegranate peel extract counteracted the high-fat-induced expression of inflammatory markers in both the colon and visceral adipose tissue. These findings suggest that pomegranate constitutes a promising food in the control of atherogenic and inflammatory disorders associated with diet-induced obesity. Considering the low bioavailability of pomegranate polyphenols, the bifidogenic effect observed after pomegranate peel extract consumption suggests the involvement of the gut microbiota in the management of host metabolism by phenolic compounds present in this extract (Neyrinck et al. 2013). Proanthocyanidin-rich

Table 2. *In vitro, in vivo* and clinical studies assessing the effects of phenolic compounds or their extracts in the host.

References	Phenolic compound or extract	Evaluated parameters	Main outcomes
			In vitro studies
Del Bo et al. (2016)	Anthocyanins and phenolic acids	Counteract lipid accumulation in macrophages derived from monocytic THP-1 cells.	Lipid accumulation was reduced in all tested concentrations of anthocyanin-rich fractions with a maximum reduction at 10 μg/mL (−27.4%). The phenolic acid-rich fraction reduced lipid accumulation only when tested at concentrations from 0.05 to 0.3 μg/mL.
Kuntz et al. (2017)	Anthocyanins	Modulation of pancreatic cancer cell migration.	Reduced cell migration, which was associated with reduced levels of endogenously generated reactive oxygen species, concomitant with reduced NF-κB, MMP-2 and MMP-9 mRNA expression.
			Experimental studies
Qiao et al. (2014)	Resveratrol	Gut microbiota composition, glucose and lipid metabolism.	Resveratrol (200 mg per kg per day) significantly reduced both body and visceral adipose weight and reduced blood glucose and lipid levels in high-fat diet mice. Resveratrol improves gut microbiota dysbiosis induced by high-fat diet, including increased Bacteroidetes-to-Firmicutes ratios, significantly inhibiting the growth of *Enterococcus faecalis* and increasing the growth of *Lactobacillus* and *Bifidobacterium*.
Morales-Cano et al. (2014)	Quercetin	Pulmonary arterial hypertension.	Quercetin decreased pulmonary arterial pressure, right ventricular hypertrophy and muscularization of small pulmonary arteries. Biomarkers of pulmonary arterial hypertension, such as downregulated expression of lung BMPR2, Kv1.5, and Kv2.1 and upregulated survivin, endothelial dysfunction and hyper responsiveness to 5-HT, were not affected by quercetin.
Etxeberria et al. (2015)	Trans-resveratrol and quercetin	Counteract gut microbiota dysbiosis produced by high-fat sucrose diet.	Administration of both polyphenols together prevented body weight gain and reduced serum insulin levels. Individual supplementation with trans-resveratrol and quercetin reduced serum insulin levels and insulin resistance.
Song et al. (2016)	Anthocyanins	Effects on high-fat diet-induced liver steatosis and underlying molecular mechanism.	Supplementation with anthocyanins alleviated high-fat diet-induced liver steatosis in mice. Microarray analysis of hepatic gene expression profiles indicated that SWCN treatment changed the expression profiles of 1119 genes, which were enriched in different pathways, such as PPAR signalling pathway, steroid biosynthesis, fatty acid metabolism, and biosynthesis of unsaturated fatty acids.
			Clinical studies
Li et al. (2013)	Flavonoid and stilbene	Cardiovascular risk factor.	Higher daily consumption of anthocyanidins was associated with elevated serum high-density lipoprotein cholesterol (HDL-C), and higher total flavonoid and flavonol intakes were associated with lower serum triglyceride (TG) concentrations and TG/HDL-C in female subjects.
Igwe et al. (2017)	Anthocyanin-rich plum juice	Antihypertensive effect and acute cognitive function.	Reduction in blood pressure and cardiovascular responses was observed in younger and older adults. Higher reductions in blood pressure were observed in the older age group.
Theodotou et al. (2017)	Resveratrol	Antihypertensive effects and function of hepatic enzymes.	The addition of resveratrol to standard antihypertensive therapy was sufficient to reduce blood pressure to normal levels without the need for additional antihypertensive drugs. Micronized formulation of resveratrol reduced plasma levels of glutamate-pyruvate transaminase and gamma GT, indicating prevention of liver damage.

extracts have also been shown to increase the *Bifidobacterium* faecal population in humans (Dolara et al. 2005). A high *Bifidobacterium* faecal population has been tentatively related to improved glucose tolerance and decreased inflammatory status in preclinical and clinical findings (Laitinen et al. 2009; Luoto et al. 2010; Moya-Pérez et al. 2015).

The consumption of grape polyphenols has been shown to attenuate adverse health consequences associated with the consumption of a high-fat diet, especially the effect on the intestinal microbiota (Collins et al. 2016). Modulation of the intestinal microbiota by high-fat diets has negatively impacted the intestinal permeability and expression of genes encoding proteins, such as those exerting an important role in intestinal barrier function (Cani et al. 2008; Kim et al. 2012). Long-term supplementation with polyphenol-rich tea-green powder in combination with *L. plantarum* DSM 15313 promoted an increased *Lactobacillus* population in the intestine and attenuated the inflammation induced by a high-fat diet in mice (Axling et al. 2012). Consumption of high-flavonoid apple was associated with decreases in some inflammation markers and changes in the gut microbiota when fed to healthy mice (Espley et al. 2014). The administration of polyphenol-rich juçara pulp reduced the pro-inflammatory status induced by a maternal diet with a high intake of *trans*-fatty acids during pregnancy and lactation, restoring the faecal population of *Bifidobacterium* in rat offspring (Morais et al. 2015).

Curiously, no alterations were observed in the intestinal microbiota of healthy rodents after 10-week administration of anthocyanin-rich grape and bilberry (80:20) juice. These results suggested that the pre-installed inflammatory condition and interactions with other factors could influence modulation of the intestinal microbiota by the polyphenols present in the tested juice (Graf et al. 2013). An early study observed that supplementation with cranberry procyanidins increased the production of intestinal mucus in rats. Increased mucus production has been associated with modulation of the gut microbiota, increasing the population of selected beneficial bacteria (Pierre et al. 2013).

The consumption of polyphenol-rich blueberries previously fermented with *L. plantarum* DSM 15313 reduced blood pressure in hypertensive rats after a 2-week treatment. Furthermore, the ingestion of the fermented blueberries juice reduced alanine aminotransferase and affected positively the composition of gut microbiota in healthy rats (Ahrén et al. 2015). However, the same probiotic was administered as a blueberry fermented product to humans, and no reduction in blood pressure of adults with hypertension was observed after three-month consumption (Xu et al. 2015). The tested product did not affect the diversity or composition of the oral and faecal microbiota. Moreover, the oral and faecal microbiota remained stable over the three-month intervention period.

Phenolic compounds from cranberry extracts administered to rats alone or in combination with *Bacillus subtilis* CU1 over nine weeks increased and decreased the population of *Barnesiella* (member of the phylum *Bacteroidetes*) and *Oscillibacter* (member of the phylum *Firmicutes*), respectively, which are bacterial genera strongly associated with intestinal health (Dudonné et al. 2015). Most of the phenolic compounds identified in rat plasma following cranberry extract administration were microbial metabolites produced during colonic microbial degradation. These findings indicated that the observed beneficial effects in rats were exerted by intestinal microbial-derived metabolites in tissues rather than by original phenolics present in cranberry extract. The data of this study also suggested that the bioavailability of phenolic compounds present in cranberry extract could have been increased by an additional positive effect exerted by *B. subtilis* CU1 ingestion on intestinal microbiota composition, which increased the amounts of active microbial metabolites in plasma.

Patients with metabolic syndrome who consumed polyphenol-rich red wine presented increased faecal numbers of bacteria belonging to *Bifidobacterium* and *Lactobacillus* genus (intestinal barrier protectors) and *Faecalibacterium prausnitzii* and *Roseburia* (butyrate producing) in addition to decreased populations of *E. coli* and *Enterobacter cloacae* after a 30-day consumption period (Moreno-Indias, et al. 2016). Proanthocyanidin-rich extracts have also been shown to increase the *Bifidobacterium* faecal population in humans (Dolara et al. 2005). A high *Bifidobacterium* faecal population has been tentatively related to improved glucose tolerance and decreased inflammatory status in preclinical and clinical findings (Laitinen et al. 2009; Luoto et al. 2010; Moya-Pérez et al. 2015). A randomized, double-blind, placebo-controlled trial evaluating the gut microbiota composition of overweight men and women after 12-week combined supplementation with epigallocatechin-3-gallate and resveratrol (282 and 80 mg/day, respectively) found gender-dependent effects. While epigallocatechin-3-gallate + resveratrol supplementation for 12 weeks reduced the population of *Bacteroidetes* in the faecal samples of men, no effects were observed in women (Most et al. 2017). The combined use of probiotics and phenolics has been cited as an interesting approach to potentiate the beneficial health-related effects of phenolic compound ingestion (or of their metabolites) (Dudonné et al. 2015; de Brito Alves et al. 2017).

4.2. Beneficial effects of phenolic compound metabolites produced by the gut microbiota

A range of different biological activities originally attributed to dietary phenolic compounds has been re-directed to absorbable metabolites derived from the microbial biochemical transformations of these compounds (Espín et al. 2017; González-Sarrías et al. 2017b). The biotransformation of naturally occurring phenolic compounds has been mostly examined in *in vitro* models using faecal fermentation (Parkar et al. 2013; Kaprasob et al. 2017). Additionally, the results of early studies have suggested that the health benefits of phenolic compounds could be related to increased generation of short chain fatty acids as a consequence of microbial metabolism (Wong et al. 2006; Vendrame et al. 2011).

In general, the molecular mechanisms underlying the action of dietary phenolic compounds and their microbe-derived metabolites seem to be similar. Therefore, the identification of specific bioactive metabolites, along with aspects related to the bioavailability, metabolism and tissue distribution of parent dietary phenolic compounds, could be valuable for understanding the action of bioactive phenolic gut metabolites (Ekbatan et al. 2016). However, the association between the presence of a

specific gut metabolite and the related health effects promoted by a dietary phenolic compound has also been little explored.

Ellagitannins, lignans, isoflavones and flavanones have been shown to be suitable substrates for the intestinal microbiota, and the systemic effects initially attributed to these compounds have been related to their microbial metabolites (González-Sarrías et al. 2017b). This inference is supported by the ability of microbial communities to produce specific metabolites from different polyphenol groups, including isoflavones (Frankenfeld 2017), lignans (Lagkouvardos et al. 2015; Clavel et al. 2016), ellagitannins (Tomás-Barberán et al. 2016) and proanthocyanidins (Takagaki and Nanjo 2015). Additionally, these metabolites have been considered biomarkers for the presence of specific microorganisms in the intestine (Tomás-Barberán et al. 2016).

Dihydroxylated phenolic acids (e.g., 3,4-dihydroxyphenylpropionic acid, 3-hydroxyphenylpropionic acid and 3,4-dihydroxyphenylacetic acid) produced during microbial metabolism of proanthocyanidins showed remarked anti-inflammatory properties, reducing the release of TNFa-α, IL-1b and IL-6 in lipopolysaccharide-stimulated peripheral blood mononuclear cells in healthy individuals. The researchers suggested the tested phenolic microbial metabolites as promising alternative therapeutic agents for immune-inflammatory diseases (e.g., atherosclerosis) (Monagas et al. 2009) and for directing the inflammatory response to bacterial antigens implied in chronic inflammation and autoimmune disease aetiology (e.g., inflammatory bowel disease) (Tuohy et al. 2012).

p-hydroxyphenylacetic acid has been shown capable of decreasing the production of reactive oxygen species in neutrophils, being suggested as a biomarker in sepsis progression. During the development of bacteremia and purulent foci in infections caused by *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, p-hydroxyphenylacetic acid has been shown able to enter directly into the bloodstream and inhibit the phagocytic activity of neutrophils (Beloborodova et al. 2012).

A pomegranate ellagitannin-rich extract showed anti-inflammatory activities and preserved the permeability of the colonic wall in a colitis-induced mouse model (Larrosa et al. 2010). Interestingly, the administration of urolithin (ellagitannin metabolite) exerted stronger effects than the tested pomegranate extract (Larrosa et al. 2010). The findings of this study revealed that when pomegranate polyphenols were not detected in the mouse colon, urolithin A was the most abundant metabolite found therein. This result reinforced the possibility that urolithin A was the active anti-inflammatory compound in tested pomegranate extract (Larrosa et al. 2010).

A decrease in cardiovascular risk in patients receiving a red-wine intervention was partially related to the microbial proanthocyanidins metabolite 4-hydroxyphenylacetate (Sánchez-Patán et al. 2012; Vázquez-Fresno et al. 2016). The selective improving effects of an ellagitannin-rich pomegranate extract on cardiometabolic biomarkers (e.g., total cholesterol, LDL cholesterol and HDL cholesterol) in obese individuals was related to the microbial metabolite urolithin B (González-Sarrías et al. 2017b). Although there has been no clear definition of enterolignan-producing phenotypes, observational studies have related urinary enterolactone and enterodiol, which are produced by specific bacterial communities, to improvements in cardiovascular risk markers, such as plasma lipid levels, blood pressure and inflammatory parameters (Sun et al. 2014).

Equol [7-hydroxy-3-(4′-hydroxyphenyl)-chroman] is the most well-known phenolic microbial metabolite with a variety of biological properties (Setchell and Clerici 2010; Liu et al. 2014). There is an estimate that approximately 30–50% of humans have intestinal microbiota composition and function sufficient to convert isoflavone daidzein to equol (Bolca et al. 2007). Although probiotic bacteria have already been shown capable of transforming daidzein in equol (Elghali et al. 2012), the strategies applied to stimulate equol production through supplementation with probiotic bacteria have been generally unsuccessful (Lampe et al. 2001; Uehara et al. 2001; Bonorden et al. 2004). Dietary factors may also influence equol production in healthy adults, including a high intake of polyunsaturated fatty acids, maltose and vitamins A and E (Setchell et al. 2013).

After ingestion of aronia-citrus juice, the flavanone metabolites in control and triathlete volunteers were glucuronides, sulphates and sulpho-glucuronides. The total excretion of flavanones was five-fold higher in triathletes compared to control volunteers. The increases in homoeriodictyol metabolites in triathletes compared to control volunteers may suggest enhanced gut microbiota metabolism induced by physical exercise (Medina et al. 2012).

Additional knowledge on the mechanisms underlying the health effects attributed to dietary phenolic compounds should enable optimization of the use of these compounds through the modulation of the intestinal microbiota and consequently the production of microbial metabolites, which may increase the biological effects attributed to dietary parent phenolic compounds.

5. Effects of phenolic compounds on probiotic survival in foods

The technological characteristics of probiotics are primarily related to their ability to survive during food processing and storage and to offer distinct nutritional, physicochemical and sensory properties to the final product (Salvucci et al. 2016; Corbo et al. 2017). The survival of probiotics is strongly influenced by the physicochemical characteristics of foods, which are partially driven by the ingredients used in food formulations (Silva et al. 2017b).

The growth and metabolism of *L. casei* LC2W, *L. casei* BD-II and *L. casei*-01 were enhanced by the incorporation of rich-phenolic ingredients in cow milk, such as green tea infusion. Higher bacterial counts, reduced fermentation time, abundant production of flavour compounds and high release of free amino acids were achieved during the fermentation of milk supplemented with green tea using the tested *L. casei* strains (Ma et al. 2015). The incorporation of grape pomace extract into goat milk that was further fermented with *L. acidophilus* LA-05 and *L. rhamnosus* HN001 increased the survival of the added probiotics until 14 days of storage under refrigeration. The total phenolic content was increased in fermented milk containing grape pomace extract. Flavour, colour and overall acceptability were increased in fermented milk containing grape pomace extract (Santos et al. 2017).

Pleurotus ostreatus aqueous extract, which is rich in phenolic compounds, was incorporated into cow milk to produce a yogurt with distinct functional and rheological characteristics. Incorporation of *P. ostreatus* aqueous extract into milk increased the counts of *Streptococcus thermophilus* and *L. bulgaricus* over time. Yogurts containing the *P. ostreatus* aqueous extract exhibited lower syneresis and firmness, but increased adhesiveness, springiness and cohesiveness, in addition to presenting higher phenolic content and higher antioxidant properties during storage under refrigeration. These results indicated that *P. ostreatus* aqueous extract could be used to manufacture low fat yogurt with potential functional properties in addition to presenting improved rheological characteristics (Vital et al. 2015).

The survival of *L. acidophilus* ATCC 1643 in a cow milk-based drink increased with supplementation with aqueous apple peel phenolic extract or purified polyphenols over a 50-day refrigeration storage period. However, apple skin phenolic extract promoted the growth of *L. acidophilus* more than either of the tested polyphenols, with the exception of rutin. These findings indicate the potential use of apple skin as a source of polyphenols to enhance probiotic bacteria functionality in dairy foods in addition to adding value to this waste stream agro-industrial material (Shinde et al. 2015).

A study observed that the survival of *L. casei* T4 sharply decreased in cherry juice (pH 2.6) in up to 7 days of refrigerated storage. Interestingly, this strain grew well for up to 28 days of refrigerated storage when the pH of the cherry juice was adjusted to 3.5. The phenolic content and antioxidant activity slightly decreased in cherry juice with higher bacterial counts, indicating that the added probiotic was able to metabolize the phenolic compounds of cherry juice. The incorporation of *L. casei* T4 positively impacted the flavour, odour and general acceptance of cherry juice (Nematollahi et al. 2016). The slight decrease in phenolic content in cherry juice containing *L. casei* T4 was associated with both the reduced metabolic activity of lactobacilli under cold temperatures and the presence of dissolved oxygen in juice samples, which can cause the oxidation of phenolic compounds (Prasawang et al. 2010; Nematollahi et al. 2016).

Grapes are rich polyphenol sources and recognized for their health benefits (Morelli and Prado 2012). Yogurt formulations containing different concentrations of an Isabel grape preparation showed high counts of *L. acidophilus* LA-05 over 28 days of refrigerated storage. The addition of Isabel grape preparation positively affected the colour, viscosity and sensory acceptance of yogurt formulations (Silva et al. 2017b). A reduction in phenolic content and an increase in carotenoid and flavonoid content were observed in butiá ice-cream containing *B. lactis* Bl-04 over 90 days of frozen storage. Panellists reported good acceptance and purchase intention with the probiotic butiá ice-cream containing *B. lactis* Bl-04. The combination of a well-known probiotic strain and phenolic-rich butiá pulp was cited as a possible approach to add health-related functional values to the product (Cruxen et al. 2017).

Chocolate presents a variety of bioactive compounds, such as polyphenols and flavonoids (e.g., catechin, epicatechin and procyanidin), with strong antioxidant activities (Todorovic et al. 2015). Stimulating effects on the growth of *L. casei* ATCC 334, *L. rhamnosus* ATCC 11443, *L. plantarum* ATCC 39542, *L. acidophilus* ATCC 4356 and *B. subtilis* PIC 620 were observed in cow milk containing 3% cocoa powder. In contrast, the growth of *E. coli* EDL 933, *Salmonella* Typhimurium LT2 and *L. monocytogenes* LM2 was inhibited in this product (Peng et al. 2015). The capability of encapsulated *L. casei* NCDC 298 to survive in milk chocolate was also evaluated. *Lactobacillus* counts remained > 8 log CFU/g in milk chocolate until 60 days of refrigeration storage. Moreover, milk chocolate containing encapsulated lactobacilli presented good acceptance over the monitored storage time period (Mandal et al. 2013). A study that added lyophilized *L. rhamnosus* GG, *L. paracasei* F19, *L. casei* DG or *Lactobacillus reuteri* DSM 17938 in dark chocolate with 80% cocoa stored at 18 °C observed that probiotic survival was strain-dependent. In this study, the phenolic contents in dark chocolate did not seem to influence probiotic survival over time. Dark chocolate containing the probiotics presented good acceptance during a 90-day storage period (Succi et al. 2017).

L. acidophilus NCFM® and *B. lactis* HN019 were also incorporated into milk and dark chocolate. *L. acidophilus* NCFM® presented higher survival rates than *B. lactis* HN019 in both chocolate types. Despite of the occasionally noted sandiness, the sensory properties of the chocolates were not altered during storage (Laličić-Petronijević et al. 2015). Another study that incorporated encapsulated *L. acidophilus* NCFM® and *B. lactis* HN019 into milk and dark chocolate observed that these strains tolerated the product manufacturing process and maintained high viable counts during 14 months of storage at 15°C (Klindt-Toldam et al. 2016). *L. casei* 01 and *L. acidophilus* LA-05 showed high viable counts (> 6 log CFU/g) in dark chocolate for up to 60 days of storage at 4 °C, followed by milk (10% cocoa) and white chocolate (0% cocoa). Incorporation of the tested probiotics did not affect the milk and white chocolate sensory characteristics (Kemsawasd et al. 2016). The counts of *L. acidophilus* NCFM® and *B. lactis* HN019 did not differ in milk (27% cocoa) and dark chocolate (75% cocoa) during a 180-day storage period at 4 °C (Laličić-Petronijević et al. 2015).

Overall, the data from available literature reveal that the presence of phenolic compounds could enhance the survival of probiotics in different food matrices. Additionally, the interaction of probiotics and phenolic compounds could improve the general quality characteristics of foods and potentiate the health beneficial effects of both components.

6. Conclusion and future perspectives

Based on most of the available literature, the interactions among phenolic compounds and beneficial microorganisms, either those forming the gut microbiota or those characterized as probiotics, is indeed an emerging key factor in achieving the health-promoting effects induced by these components. The findings of the retrieved studies strongly indicate mutually beneficial interactions among dietary phenolic compounds and probiotic strains. The gut microbiota and selected probiotic strains have been shown capable of improving the metabolism and bioavailability of phenolic compounds. In turn, phenolic compounds may positively modulate the gut microbiota composition and protect probiotic bacteria from the harsh

conditions found during gastrointestinal passage and in different foods. Notably, the varied health benefits associated with the ingestion of specific phenolic compounds among different individuals seem to be a consequence of inter-individual variability in the gut microbiota composition and function, which may determine the metabolism of phenolic compounds, production of specific phenolic metabolites and bioavailability. However, there has been little clinical evidence on the beneficial effects caused by the interaction of phenolic compounds and probiotics on the host. Attention must be focused on the development of *in vitro* and experimental findings to confirm the beneficial interactions among different phenolic compounds and selected probiotic strains. Finally, foods containing combinations of phenolic compounds and probiotics could be promising added-value products for the food industry, considering that they have already demonstrated good acceptability and that there are well-known health benefits associated with the consumption of these bioactive components.

Conflict of interest

The authors declare no conflict of interest related to the content of this manuscript.

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