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REVIEW

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Probiotic fermentation of polyphenols: potential sources of novel functional foods

Rohit Sharma[1*], Bhawna Diwan[1], Brij Pal Singh[2] and Saurabh Kulshrestha[1]

Abstract

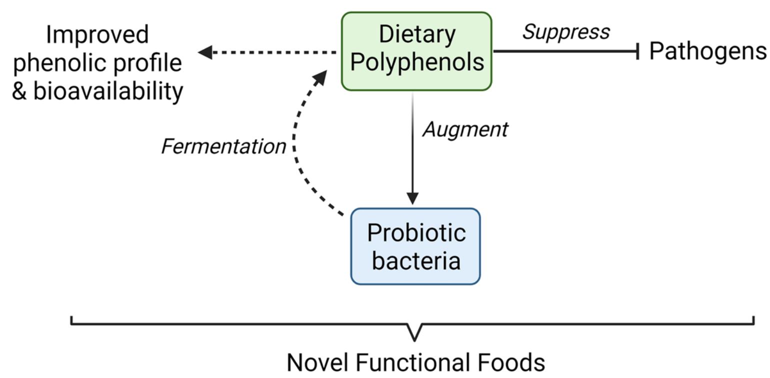
Fermented functional food products are among the major segments of food processing industry. Fermentation imparts several characteristic effects on foods including the enhancement of organoleptic characteristics, increased shelf-life, and production of novel health beneficial compounds. However, in addition to macronutrients present in the food, secondary metabolites such as polyphenols are also emerging as suitable fermentable substrates. Despite the traditional antimicrobial view of polyphenols, accumulating research shows that polyphenols exert differential effects on bacterial communities by suppressing the growth of pathogenic microbes while concomitantly promoting the proliferation and survival of probiotic bacteria. Conversely, probiotic bacteria not only survive among polyphenols but also induce their fermentation which often leads to improved bioavailability of polyphenols, production of novel metabolic intermediates, increased polyphenolic content, and thus enhanced functional capacity of the fermented food. In addition, selective fermentation of combinations of polyphenol-rich foods or fortification with polyphenols can result in novel functional foods. The present narrative review specifically explores the potential of polyphenols as fermentable substrates in functional foods. We discuss the emerging bidirectional relationship between polyphenols and probiotic bacteria with an aim at promoting the development of novel functional foods based on the amalgamation of probiotic bacteria and polyphenols.

Keywords: Probiotics, Polyphenols, Fermented Foods, Lactic acid bacteria, Tea

*Correspondence: rohit25sharma@gmail.com

[1] Faculty of Applied Sciences & Biotechnology, Shoolini University of Biotechnology and Management Sciences, Solan 173229, India
Full list of author information is available at the end of the article

Graphical abstract



Introduction

Human beings have been consuming fermented foods as a staple diet since ancient times. Historically, fermentation presented an effective way of food preservation and as such several different types of foods such as dairy, vegetables, meat, cereals, and fruits have been fermented (Tamang et al. 2020). However, today there is a renewed interest in understanding and developing novel fermented foods among nutritionists, biologists, and consumers alike since fermented foods are rich in unique bioactive ingredients which may be implicated in their superior health beneficial attributes (Şanlier et al. 2019). Several types of indigenous fermented foods are consumed in various cultures and societies through natural fermentation, and these foods are often novel sources of desirable probiotic strains which can then be utilized for the industrial preparation of other fermented food products (Harnentis et al. 2020; Surve et al. 2022). As such, the need for a careful interpretation and understanding of fermented foods was recently emphasized and fermented foods have now been redefined as "foods made through desired microbial growth and enzymatic conversions of food components" (Marco et al. 2021). Fermentation imparts several characteristic physicochemical and biological changes in foods such as improved shelf life, enhanced organoleptic characteristics, and increased bioavailability of vitamins and minerals. In addition, both preclinical and clinical studies have demonstrated that fermented foods are effective against chronic human disorders such as cancer (Bermejo et al. 2019; Zhang et al. 2019), cardiovascular disorders (Companys et al. 2021; Zhang et al. 2020), gut microbial dysbiosis (Stiemsma et al. 2020), obesity (Mohammadi et al. 2021), diabetes (de Almeida Souza et al. 2020), inflammatory aggravation (Wastyk et al. 2021), as well as immunosenescence (Sharma et al. 2014) ultimately resulting in improved organismal lifespan (Das et al. 2020).

During fermentation, microorganisms metabolize the nutrients present in the food and convert them into simpler and often characteristically unique components. For instance, bioactive peptides are often produced as a result of protein degradation by microorganisms during fermentation which are associated with several health-beneficial effects (Chakrabarti et al. 2018). Similarly, exopolysaccharides are also synthesized by microorganisms during the fermentation of carbohydrates that contribute to the flavor and pharmacological effects of fermented foods (Lynch et al. 2018). However, it is important to consider that primary macronutrients are not the only substrates of microbial fermentation in foods. Accumulating evidence suggests that secondary plant metabolites, such as polyphenols, may have a deeper association with fermenting microorganisms, particularly with probiotic bacteria (Piekarska-Radzik & Klewicka 2021). In fact, a bidirectional relationship between polyphenols and probiotic bacteria, including in the context of fermented food and health, is rapidly gaining attention (Banerjee & Dhar 2019; Kawabata et al. 2019). The present paper intends to apprise the readers regarding current developments in probiotic-mediated fermentation of polyphenol-rich foods. We first provide an overview of macronutrient fermentation and then specifically review the existing knowledge on polyphenolic fermented foods. The mutual relationship between polyphenols and probiotic bacteria as well as the applicability and usefulness of fermented polyphenolic foods is then deliberated with an emphasis on the development of novel functional food products.

Microbial fermentation of food macronutrients

Fermentation can be broadly classified into two types depending on the type of fermenter microorganisms: spontaneous fermentation and starter culture-dependent fermentation. Spontaneous fermentation occurs when microorganisms are naturally present in the raw food or in the processing environment such as in *dahi* or kimchi (Dimidi et al. 2019). On the other hand, starter culture fermentation employs direct inoculation of specific microorganisms into food materials for more predictable and desired changes in the fermented food (García-Díez & Saraiva 2021). Starter cultures are extensively used in the food industry as they are often associated with characteristic sensory, nutritional, and health beneficial changes (García-Díez & Saraiva 2021). Regardless of the source, microbial fermentation extensively modifies the chemical profile of the fermented food product due to the metabolism of various macronutrients present in the food. To achieve this, microorganisms have several characteristic enzymes such as proteases, peptidases, ureases, polysaccharide degrading enzymes, lipases, amylases, esterases, and phenoloxidases that might otherwise be lacking in the host (Chugh & Kamal-Eldin 2020). Raw food material consists of diverse carbohydrates including monosaccharides, disaccharides, and polysaccharides which are used as a substrate by probiotic bacteria. Different species of probiotic bacteria can metabolize different types of carbohydrates and thus may be utilized for specific and varied applications in the food industry (Hedberg et al. 2008). Probiotic bacteria often express several carbohydrates metabolizing enzymes such as glycosyl hydrolases, sugar ABC transporters, and phosphoenolpyruvate and phosphotransferase systems which can act on carbohydrates of both plant and animal origin (Pokusaeva et al. 2011). Carbohydrates are primarily used by probiotic bacteria for meeting energy requirements and are converted to organic acids such as short-chain fatty acids (SCFAs) while the non-digestible oligosaccharides such as hemicellulose and pectins also act as prebiotics for the growth of probiotic bacteria (Kelly et al. 2021; Wang, Wu, Lv, et al. 2021). The SCFAs are of particular importance and their high levels in fermented foods are often associated with improved health benefits due to their documented ability to alter cell signaling pathways (Tan et al. 2014), improve gut epithelial barrier integrity (Silva et al. 2020), and suppress pro-inflammatory immune responses in the gut (Annunziata et al. 2020; Parada Venegas et al. 2019). In addition, exopolysaccharides are produced by bacteria during carbohydrate fermentation which are significant determinants of physicochemical characteristics of fermented foods including their texture, flavor, and shelf-life (Baruah et al. 2022). Further, specific exopolysaccharides can act as prebiotics and can impart health beneficial effects to the host including the modulation of the immune system and the gut microbiome (Oerlemans et al. 2021).

In addition to carbohydrates, the degradation of proteins is an important factor in determining the quality and nutritive value of fermented foods, especially dairy products. During fermentation, large proteins are catabolized into smaller fragments, often yielding bioactive peptides with anti-thrombogenic, anti-oxidant, anti-hypertensive, and anti-inflammatory activities that have been validated in numerous *in vitro* and preclinical studies (Daliri et al. 2017; Daroit & Brandelli 2021; Karami & Akbari-Adergani 2019). Several different types of bioactive peptides, depending on the food source and probiotic microorganisms used, have been identified and are curated in a recently developed database (Chaudhary et al. 2021). Dairy proteins (Ali et al. 2022; Fan et al. 2019), meat proteins (Xing et al. 2019), as well as vegetable proteins (Chatterjee et al. 2018; Montesano et al. 2020) have been well characterized for their fermented bioactive peptides. In addition, fermentation of specific proteins (e.g., casein) can also alleviate the potential allergenicity of certain food constituents, such as milk and its products, thereby improving their general acceptability in vulnerable populations (Anggraini et al. 2018; Mu et al. 2021). Similarly, probiotic microorganisms can improve the overall digestibility and nutritive value of proteins in foods by the breakdown of complex storage proteins into more absorbable soluble forms (Skalickova et al. 2022). Further, probiotic bacteria can metabolize amino acids through processes such as deamination and decarboxylation that ultimately aid in the regulation of biogenic amines production in foods that are otherwise considered toxic (Fong et al. 2020). In a randomized clinical trial on healthy subjects, co-ingestion of pea proteins with strains of probiotic *Lactobacillus paracasei* for two weeks significantly improved the absorption of amino acids such as methionine, histidine, valine, leucine, isoleucine, tyrosine and thus enhanced the nutritive value of consumed food (Jäger et al. 2020).

Lipids are important determinants of fermented food flavor and bioactivity. Studies have shown that fermentation can affect the composition of short as well as long-chain fatty acids such as butyric acid, oleic acid, palmitic acid, and conjugated linoleic acid. This is primarily attributed to lipolysis and proteolysis enzymatic activities of specific probiotic bacteria (Feng et al. 2021). For example, milk fermented with probiotic *Lactobacillus acidophilus* and *Lactobacillus casei* resulted in increased levels of butyric and linoleic acids (Yadav et al. 2007). The addition of specific probiotic isolates has been recently demonstrated to improve the content of free fatty acids and the flavor of fermented sausage (Wang, Hou et al. 2022). Another study observed explicit changes in the fatty acids profile of germinated beans after fermentation with *Lactobacillus* strains (Ziarno et al. 2020). It was also reported that increasing the fat content in milk significantly impacted the fermented fatty acid profile as evidenced by increased bacterial lipolysis, proteolysis, and the synthesis of novel volatile compounds (Bao et al. 2016). Together, these observations suggest that fermentation is a key way of naturally improving the fatty acid content in the foods that can be utilized to produce functional foods with higher nutritive value (Annunziata et al. 2020). Figure summarizes the effects of probiotic fermentation on metabolism of major macronutrients present in foods (Fig. 1).

Probiotic fermentation induces qualitative and quantitative changes in phenolic profile

Polyphenols are a diverse class of secondary metabolites that are widely distributed in fruits, vegetables, spices, nuts, grains, and legumes. Chemically, these molecules contain at least one aromatic ring conjugated with one or more hydroxyl groups based on which polyphenols are further classified into several classes such as flavonoids, phenolic acids, stilbenes, and lignans (Tijjani et al. 2020). Whether naturally rich or fortified, foods rich in polyphenols are highly valued and their consumption has long been associated with health-beneficial effects (Cory et al. 2018; McDougall, 2017). This is primarily attributed to the strong antioxidant potency of polyphenols that have been demonstrated to augment cellular redox homeostasis in both animal and human studies (Basu et al. 2013; Hurst et al. 2020; Pandey & Rizvi 2009; Wang et al. 2021). Natural polyphenols are generally considered anti-microbial, however, accumulating evidence suggests a deeper and rather bidirectional association between probiotic bacteria and polyphenols with implications for the development of novel fermented functional foods (Ray & Mukherjee 2021). It is emerging that probiotic fermentation of polyphenols can biotransform complex polyphenols into simpler, free, and more soluble compounds that ultimately result in enhanced levels of total bioactive compounds as well as improved overall bioavailability of polyphenols in the fermented product (Escrivá et al. 2021; Hole et al. 2012; Hwang et al. 2021) On the other hand, the presence of polyphenols in foods may have a certain degree of advantage for the specific growth of probiotic bacteria since polyphenols appear to exhibit differential growth-promoting effects on the microbial population *per se* (Alves-Santos et al. 2020; Pacheco-Ordaz et al. 2018). In addition, polyphenols are rather poorly absorbed in the small intestine and are passed on to the colon in large proportions wherein they are extensively metabolized by the gut microflora into low molecular weight phenolic acids which are then taken up by the portal vein to the liver for further metabolism (Marín et al. 2015; Scalbert et al. 2002). The lower rate of absorption of polyphenols results in their prolonged persistence in the gut which permits extensive

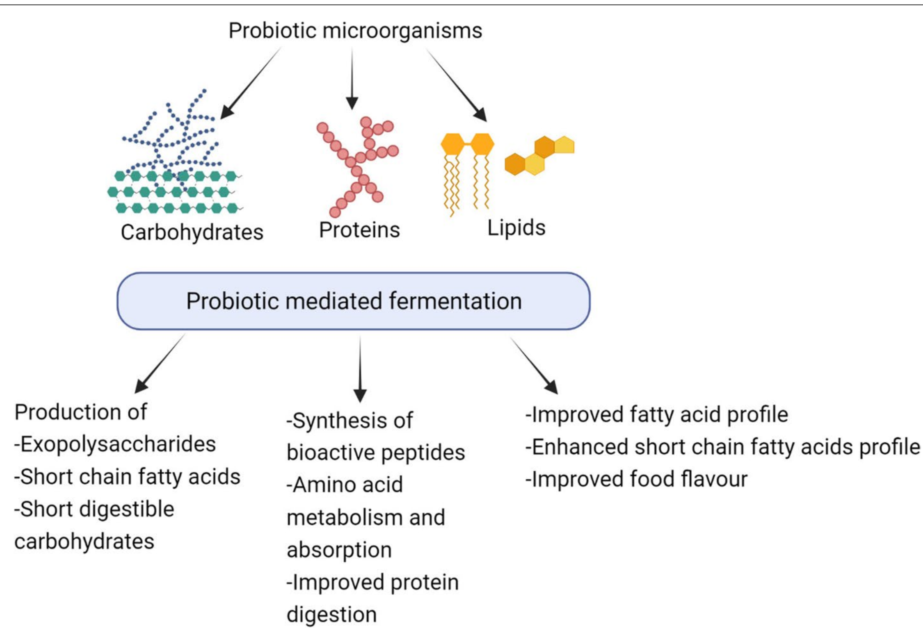


Fig. 1 Effect of probiotic bacteria on the fermentation of macronutrients present in the food

biotransformation by the gut microflora. Studies have demonstrated that fermentation of various polyphenol-rich foods with specific probiotic strains can induce qualitative and quantitative changes in their polyphenolic composition and bioactivity thereby enhancing their functional food attributes as discussed below (Fig. 2).

Fermented tea

Tea is a globally popular beverage that is recognized for its sensory and health-beneficial attributes due to the high presence of polyphenols such as epigallocatechin gallate (EGCG) (Sharma & Diwan 2022). Traditionally, fermentation in tea refers to the condensation and polymerization of its phytomolecules in the presence of native enzymes, such as polyphenol oxidase, which results in the different varieties of tea such as green tea or black tea (Chacko et al. 2010). However, studies have shown that tea is also favorably fermented by probiotic microorganisms that often enhances its phytochemistry as well as bioactivity. For instance, a recent study reported that fermentation of green tea with the combination of probiotic yeast *Saccharomyces boulardii* CNCM I-745 and *Lactiplantibacillus plantarum* bacteria transformed its bioactive constituents resulting in the production of novel compounds such as methyl salicylate, geraniol, and 2-phenylethyl alcohol that also improved the aroma of tea (Wang, Sun, et al. 2022). Another recent report suggests that green tea fermented with *Levilactobacillus brevis* remarkably enhanced (up to 232.52%) the bioactive γ-aminobutyric acid content of the tea (Jin et al. 2021), while fermentation of black tea extract with *Lactobacillus acidophilus* improved its cytotoxic potential against pathogenic *E. coli* by elevating the levels of various catechins (Yang et al. 2018). Microbial fermentation of dark teas can also augment their phenolic profile as evident through an increase in glycosylated, hydroxylated, methylated, and oxidated products as compared to their native forms (Shi et al. 2021; Zhu et al. 2020). Fermentation of green and black teas with a consortium of six probiotic lactic acid bacteria (LAB) resulted in increased production of several phenolics such as pyrogallol, coumaroylquinic acid derivatives, quercetin, and kaempferol that also exhibited improved uptake by Caco-2 cells thereby indicating that fermentation could be a beneficial approach for improving phenolic bioavailability (Zhao & Shah 2016b). Similarly, an *in vivo* study in mice demonstrated that LAB fermented black tea improved the bioavailability of tea flavonoids by as much as 50%, and conferred systemic health beneficial effects by attenuating oxidative and inflammatory damage (Zhao & Shah 2016a). Another report observed that soymilk-tea beverage prepared by fermenting with a mixture of three different probiotic bacteria (*Streptococcus thermophilus*, *Lactobacillus delbrueckii* ssp. *bulgaricus,* and *Bifidobacterium longum*) resulted in increased total polyphenolic content (up to 300%) and improved 2,2-diphenyl-1-picryl-hydrazyl (DPPH) radical scavenging potential as compared to the unfermented control (Zhao & Shah 2014). Further, green tea fermented with *Lactobacilli fermentum* strain OCS19 exhibited significant alcohol metabolizing enzyme activity and protected against alcohol-induced liver injury in mice (Park et al. 2012).

Fermented fruits and vegetables

Fruits such as apples, pineapple, berries, and citrus fruits are significant sources of polyphenols which also determine their health beneficial effects (Calderón-Oliver & Ponce-Alquicira 2018). With rising consumer awareness, the development of non-dairy based sources of probiotic bacteria, such as using polyphenol-rich fruits, are increasingly becoming desirable since they are not only abundant in bioactive secondary metabolites but are also relatively cheaper and acceptable to lactose-intolerant

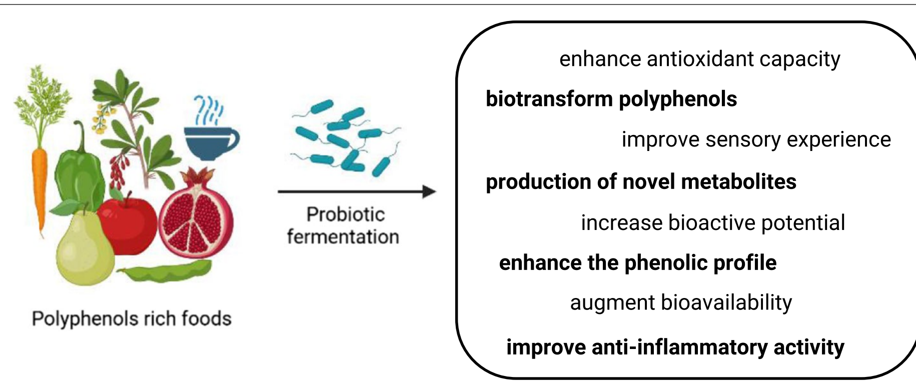


Fig. 2 Effect of fermentation with probiotic bacteria on qualitative and quantitative changes in polyphenols present in various foods

consumers (Küçükgöz & Trząskowska 2022). In particular, apples are rich in unique polyphenols such as phloretin phloridzin, and proanthocyanidins, and apple juice is considered an acceptable medium for fermentation by probiotic bacteria (Dimitrovski et al. 2015). Studies have shown that fermentation with selected probiotic strains imparts several sensory and health beneficial effects in apple juices through modification of the phenolic profile. For example, a recent study observed that fermentation of apple juice with three probiotic strains, i.e., *Lactobacillus acidophilus*, *Lactobacillus casei,* and *Lactobacillus plantarum* significantly increased its antioxidant capacity as determined by ABTS radical cation scavenging capacity and ferric reducing ability of plasma (FRAP) as well as antibacterial potency against common microbial food contaminants *Escherichia coli* and *Staphylococcus aureus* through improved phenolic and organic acid metabolism (Yang et al. 2022). Fermentation of apple juice with *Lactobacillus plantarum* improved the total flavonoid content and DPPH radical scavenging capacity (up to 36.08%) which were also accompanied by the production of new volatile compounds such as propanol, citronellol, ethyl lactate and hexyl butyrate (Li et al. 2021). Similarly, the fermentation of apple juice with six strains of LAB enhanced its antioxidant status by increasing caffeic acid and phloridzin content while several new volatiles such as alcohols and esters were also produced which improved the flavor of the fermented product (Wu et al. 2020). Another study demonstrated that apple juice fermented with *Lactobacillus plantarum* ATCC14917 resulted in increased DPPH radical and ABTS free radical cation scavenging activity by 23% and 28% respectively, as well as cellular antioxidant potency *in vitro* despite a decrease in total polyphenolic content (Li et al. 2018). Authors discovered that fermentation modified the composition of total polyphenols so that the levels of specific polyphenols such as 5-O-caffeoylquinic acid, quercetin, and phloretin with strong antioxidant activities were increased significantly after fermentation (Li et al. 2018). Another study reported that the type of apple cultivar chosen for fermentation affects the fermentation characteristics and profile which should be considered during product development approaches (Peng et al. 2021).

In addition to apples, berries have also been extensively tested for their polyphenolic and functional profile after fermentation with probiotic bacteria. Fermentation of blueberry juice with *Lactobacillus plantarum* enhanced the total phenolic content characterized by an increase in four different kinds of anthocyanins (cyanidin, petunidin chloride, pelargoridin and peonidin) that resulted in improved cytoprotective effects in the wake of oxidative damage *in vitro* (Zhang et al. 2021). Another study showed that fermentation of blueberry and blackberry juices with three different probiotic microorganisms (*Lactobacillus plantarum*, *Streptococcus thermophilus*, and *Bifidobacterium bifidum*) caused modification of the phenolic profile wherein syringic acid, ferulic acid, gallic acid, and lactic acid increased while *p*-coumaric acid, protocatechuic acid, chlorogenic acid, critic acid, and malic acid appeared to decrease albeit resulting in an overall increase in ABTS free radical cation scavenging activity and sensory quality (Wu et al. 2021). Blueberries fermented by *Lactobacillus plantarum* exhibited increased levels of phenolic acids such as malvidin 3-O-glucopyranoside, gallic acid, protocatechuic acid, catechol, chlorogenic acid, syringic acid, and epigallocatechin which collectively resulted in superior DPPH radical scavenging activity and increased anti-proliferative activity against human cervical carcinoma cells as compared to the unfermented control (Ryu et al. 2019). Fermentation of blueberry pomace with two LAB strains increased total phenols and flavonoid content (up to 300%), and its consumption in mice improved physical strength as compared to the control (Yan et al. 2019). A recent study showed that probiotic fermented blueberry juice demonstrated enhanced ABTS free radical cation scavenging activity, strong antimicrobial action against *Escherichia coli*, *Staphylococcus aureus*, and *Salmonella typhimurium* as well as *in vitro* anti-diabetic activity in HepG2 cell lines compared with non-fermented and spontaneous fermented juices (Zhong et al. 2021). When fermented with autochthonous LAB, blueberry juice resulted in a strong increase (up to 81.2%) in the phenolic content characterized by the enhanced synthesis of specific compounds such as myricetin and gallic acid (Li et al. 2021). A strain-dependent increase in the volatile profile of elderberry juice fermented with different probiotic LAB was also reported (Ricci et al. 2018). Fermentation of mulberry juice with *Lactobacillus* strains improved the phenolic content with an increase in flavanols and anthocyanins resulting in enhanced (up to 23.7%) DPPH radical and ABTS free radical cation scavenging activities (Kwaw et al. 2018). In addition to berries, other fruits such as pineapple (Nguyen et al. 2019), kiwifruit (Wang et al. 2022; Zhou et al. 2020), cherry (Frediansyah et al. 2021; Lizardo et al. 2020), guava (Bhat et al. 2015), *Ziziphus jujube* (Li, Jiang et al. 2021), pomegranate (Valero-Cases et al. 2017), pear (Wang et al. 2021), as well as citrus fruits (Tang et al. 2022) have shown the potential to be fermented by probiotic bacteria resulting in enriched phenolic profile and bioactive components. Similar to fruits, vegetable fermentation with probiotic bacteria has also been reported to augment their chemical profile and health beneficial effects. A recent study observed that LAB-mediated fermentation of vegetable juice from four crop varieties (*Brassica* *oleracea* var. *capitata*, *Brassica oleracea* var. *italica*, *Daucus carota* L., and *Beta vulgaris*) increased the total polyphenolic content as well as DPPH radical scavenging activity as compared to the unfermented juice (Lee et al. 2021). Another study reported strain-specific effects of probiotics in the fermentation characteristics of five commercially available vegetable juices using advanced NMR metabolomics (Tomita et al. 2017). Fermentation of sweet potato with various species of probiotic *Lactobacillus* improved the total phenolic content, organic acid levels, and DPPH radical scavenging capacity (Wu et al. 2012). Fermentation of capsicum with *Lactobacillus plantarum*, *Lactobacillus acidophilus*, and *Bacillus subtilis* significantly improved its efficacy to suppress high fat diet-induced obesity in C57BL/6 mice by altering the gene expression profile of lipid metabolism and hormone response (Liu et al. 2019). Further, a beverage made by combining fruits and vegetables containing apples, pears, and carrots was fermented with different LAB and the resultant fermented juice exhibited higher levels of phenols, flavonoids, and sugars, as well as antioxidant activity determined by ABTS free radical cation and DPPH radical scavenging activities (Yang, Zhou et al. 2018).

Fermented soymilk

Soymilk is an aqueous extract of soybeans that is rich in flavonoids such as isoflavones as well as phenolic acids such as syringic, chlorogenic, gallic, vanillic, and ferulic acid (Rodríguez-Roque et al. 2013). Isoflavones present in soymilk exist in two forms, i.e., the aglycones and the glucosidic conjugates. Studies have shown that the aglycone form is more readily absorbed as compared to the glucosidic form (Izumi et al. 2000), and fermentation with probiotic bacteria is considered useful for developing novel soymilk-based nutraceuticals (Sirilun et al. 2017). Previous studies have demonstrated that fermentation of soymilk with β-glucosidase producing probiotic microorganisms can increase the conversion of glucosides to aglycones resulting in enhanced bioavailability of soy phenols (Chien et al. 2006; Ding & Shah 2010; Hati et al. 2015; Rekha & Vijayalakshmi 2010, 2011). A recent study revealed soybean variety-dependent effects of *Lactobacillus acidophilus* and *Lactobacillus casei* fermentation on the isoflavones content and rheological properties of soymilk (Ahsan et al. 2022). Other reports in animal models suggest that probiotic fermented soymilk can induce antihypertensive, antioxidant, antidiabetic, and hypocholesterolaemic effects and thus may have greater functional relevance (Kumari et al. 2021). In this regard, a recent study has indicated that consumption of soymilk-fermented with *Lactobacillus delbrueckii* subsp. *delbrueckii* TUA4408L in pigs enhanced the resistance to pathogenic *Escherichia coli* infection and reduced pathogen-associated inflammatory damage in the intestinal mucosa (Suda et al. 2022). Another investigation observed that fermentation of soymilk with *Lactobacillus fermentum* CQPC04 significantly increased the isoflavones content which was associated with attenuation of oxidative damage and improved indices of antioxidant defenses in serum, liver, and brain tissues of mice in a d-galactose-induced model of accelerated aging (Zhou et al. 2021). In addition, the effectiveness of probiotic fermented soymilk consumption in the attenuation of antibiotic-associated gut microbial dysbiosis in mice has also been observed (Dai et al. 2019). Table 1 summarizes selected studies demonstrating probiotic

Table 1 Selected examples of probiotic fermentation-induced changes in phenolic rich foods

S. no	Phenolic food source	Probiotic microorganisms used	Effect of fermentation	Reference
1	Tea extracts	Lactic acid bacteria	Production of novel compounds (quercetin and pyrogallol); increased cellular bioavailability (over 90%) for EGCG	Zhao & Shah 2016a
2	Kiwifruit juice	Lactic acid bacteria	Production of novel compounds- Protocatechuic acid and catechin; increased phenolic content and antioxidant activity	Wang et al. 2022
3	Apple juice	Six lactic acid bacterial strains	Enhanced the levels of caffeic acid and phlorizin; improved aroma; increased antioxidant activity (90%)	Wu et al. 2020
4	Soymilk	*Lactobacillus fermentum*	Increased free soy isoflavones content (up to 6 folds)	Zhou et al. 2021
5	*Capsicum annuum*	*Lactobacillus plantarum, Lactobacillus acidophilus,* and *Bacillus subtilis*	Production of novel metabolites- nordihydrocapsaicin, dihydrocapsaicin, homocapsaicin and homodihydrocapsaicin	Liu et al. 2019
6	Vegetable juice from four crops	Lactic acid bacteria	Increased phenolic content (up to 24%); improved antioxidant activity	Lee et al. 2021

mediated biotransformation of polyphenolic constituents in various food items.

Polyphenols differentially modulate bacterial growth

Traditionally, polyphenols have been recognized for their antioxidant and anti-microbial attributes which are also considered useful in the natural preservation of food (Martinengo et al. 2021). However, recent studies have provided evidence of differential growth-promoting effects of polyphenols on specific microorganisms, especially considering probiotics (Ray & Mukherjee 2021). It is now becoming increasingly evident that dietary plant polyphenols suppress the growth of pathogenic bacteria while augmenting the growth of beneficial probiotic bacteria (Fig. 3). A recent study demonstrated that the presence of polyphenol-rich fractions of different medicinal plants can directly stimulate the proliferation of probiotic *Lactiplantibacillus plantarum* and yeast *Saccharomyces boulardii* while specifically suppressing the proliferation of pathogens such as *Enterococcus faecalis, Listeria monocytogenes, Staphylococcus aureus, Escherichia coli, Pseudomonas aeruginosa, and Candida albicans in vitro* (Milutinović et al. 2021). Similarly, probiotic growth-promoting and pathogen inhibitory activities of various bioactive polyphenols (catechin, and gallic, vanillic, ferulic, and protocatechuic acids) commonly present in fruits and vegetables were also reported (Pacheco-Ordaz et al. 2018). Isolated polyphenols from Oolong tea modulated the growth of human intestinal microbiota *in vitro* by inducing the proliferation of *Bifidobacterium* and *Lactobacillus/Enterococcus* species while suppressing the growth of *Bacteroides–Prevotella*, *Clostridium histolyticum,* and *Eubacterium–Clostridium* groups, but without any effect on the population of total bacteria (Zhang et al. 2013). An *in vivo* study in mice using polyphenols extracted from *Pueraria lobata* root demonstrated an increase in the proliferation of beneficial microorganisms in the gut involving *Lactobacillaceae* and *Bacteroidetes* and simultaneous suppression of the abundance of *Ruminococcaceae*, *Prevotellaceae*, and *Burkholderiaceae* (Xu et al. 2022). We also observed that green tea catechin EGCG differentially influences the growth of microorganisms *in vitro* resulting in strong suppression of pathogenic microorganisms (*Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus*, *Shigella flexneri*, and *Vibrio cholerae*) with little or no effect on the growth of probiotic LAB (*Lactobacillus rhamnosus*, *Lactobacillus planatarum*, *Lactobacillus fermentum*) (Sharma et al. 2019). Further, long-term consumption of EGCG improved the healthspan of aged mice that was associated with the amelioration of gut dysbiosis and enhanced probiotic LAB profile (Sharma et al. 2022). Although the exact reasons for the apparent differential effects of polyphenols on bacterial growth are yet unclear; however, it could be related to the polyphenol metabolizing activity of specific bacteria that may directly promote its growth as also observed in a recent study with EGCG (Xia et al. 2021). In essence, the application of polyphenols is likely to change the overall microbial community structure by inhibiting potentially pathogenic microorganisms which allows the proliferation of probiotic bacteria and thus possible

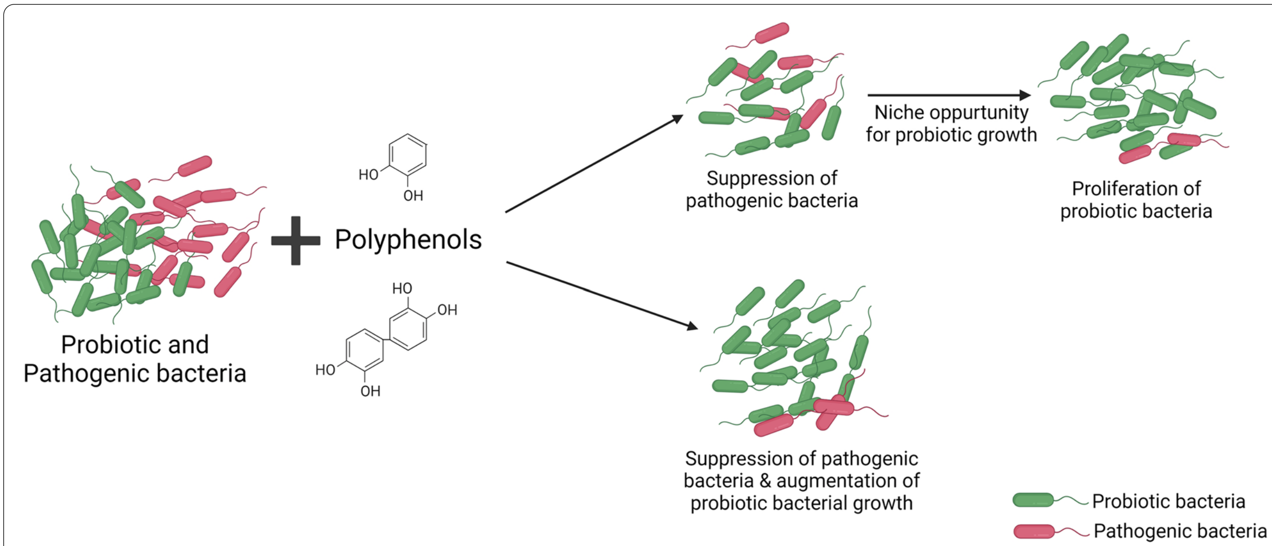


Fig. 3 Influence of food polyphenols on microbial population. Polyphenols suppress the growth of opportunistic pathogens that ultimately allows for the proliferation of probiotic bacteria. In addition, polyphenols may directly augment the growth of probiotic bacteria while still suppressing pathogenic growth thereby favorably reshaping the microbial community structure of foods

maintenance of the gut microbiota eubiosis (Fig. 3). In the latter case, polyphenols appear to act as prebiotics, and understanding this property of polyphenols is considered to be of significant application in the food industry (Nazzaro et al. 2020). It is also pertinent to mention here that the traditional oligosaccharide-based prebiotics have certain distinct disadvantages pertaining to selectivity, efficiency, and inherent bioactivity which has further highlighted the need for identifying novel non-carbohydrate sources of prebiotics and synbiotics such as based on polyphenols (Ampatzoglou et al. 2015; Gibson et al. 2017). In addition, several relatively recent *in vivo* animal studies have documented that the cytoprotective and health beneficial effects of different polyphenols in diseases such as metabolic syndrome, obesity, and colorectal cancer are often associated with the modulation of the gut microbiome characterized by augmentation of health beneficial probiotic species (Kuhn et al. 2018; Qiao et al. 2021; Wang et al. 2022; Yuan et al. 2021; Zhao et al. 2019). Furthermore, it has been demonstrated that amalgamation with polyphenols can increase the rate of probiotic bacteria survival in the gut as well as during food storage (Vodnar & Socaciu 2012), and conversely, incubation with probiotics can induce qualitative and quantitative changes in the polyphenolic profile through biotransformation ultimately resulting in enhanced biological properties (e.g., antioxidant capacity) of polyphenolic foods (López de Lacey et al. 2014). Taken together, it is reasonable to conclude that polyphenols are uniquely placed amongst substrates used for probiotic fermentation as they not only protect the probiotic bacteria from pathogenic species allowing their greater viability and proliferation, but being bioactive themselves, they may also result in particularly superior functional food formulations.

Novel functional food products based on polyphenolic fermentation by probiotics

The ability of probiotic bacteria to not only survive in polyphenol-rich conditions but also cause fermentation in various foods thereby leading to the biotransformation of native bioactive polyphenolic content has opened avenues for developing novel functional foods (Fig. 4). Based on this rationale, we systematically identified a synbiotic combination of probiotic *Lactobacillus fermentum* and green tea EGCG which on consumption resulted in enhanced antioxidant and anti-immunosenescence activities in aged mice as compared to individual treatments with EGCG or probiotic bacteria (Sharma et al. 2019). Similarly, another study observed that a novel synbiotic formulation using polyphenols of *Triphala* and three different probiotic bacterial strains (*Lactobacillus plantarum* NCIMB 8826, *Lactobacillus fermentum* NCIMB 5221, and *Bifidobacteria longum* subsp. *infantis* NCIMB 702255) was more effective in alleviating multiple markers of diet-induced diabetes and obesity in *Drosophila melanogaster* as compared to individual treatments (Westfall et al. 2018). Further, an amalgamation of polyphenol-rich wine grape seed flour and kefir-derived probiotic LAB showed synergistic anti-obesity and anti-diabetic effects in a murine model of high-fat diet-induced obesity (Cho et al. 2018). A synbiotic association between *Cudrania tricuspidata* leaf extract and probiotic *Lactobacillus gasseri* was reported which when supplemented in milk resulted in the metabolism of phenolic acids and production of novel metabolite-3,4-dihydroxy-hydrocinnamic acid and bioactive peptides that increased the free radical scavenging potential of fermented milk and also improved its *in vivo* efficacy (Ha et al. 2020; Oh et al. 2016; Oh et al. 2020). A novel dark chocolate prepared by using probiotic *Bacillus coagulans* exhibited higher levels of polyphenols while still maintaining its sensory attributes similar to the control sample (Kobus-Cisowska et al. 2019). These observations provide evidence of synbiotic attributes of polyphenols with specific probiotic bacteria which could be used for developing novel functional foods. Similarly, some studies have reported that new and improved functional food products can be developed by fermenting combinations of polyphenol-rich foods/medicinal plants with selected probiotic bacteria. For instance, combining *Houttuynia cordata* leaves with green tea and allowing the combination to be fermented by *Lactobacillus paracasei* subsp. *paracasei* resulted in higher EGCG, EGC, and chlorogenic acid levels than unfermented tea which also exhibited improved cytoprotective effects in fat cells *in vitro* (Wang et al. 2018). A functional food was prepared by fermenting a mixture of green tea extract and *Morinda citrifolia* Linn. (Noni) fruit juice by *Lactobacillus plantarum* SK15 which exhibited significantly low pH, sugar and pectin content accompanied by a concomitant increase in the levels of total phenolics (Saelee et al. 2019). A novel vegetable-fruit juice mixture was recently prepared by fermenting Jerusalem artichoke, pineapple, pumpkin, spinach, apple, and cucumber with probiotic LAB that exhibited increased viability of LAB and acceptable sensory response (Güney & Güngörmüşler 2021). Fortification of different foods with polyphenols and their subsequent fermentation with probiotic bacteria is another accepted way of increasing their functional properties. A functional milk beverage fortified with olive polyphenols and fermented with probiotic LAB was developed which demonstrated persistent LAB viability, improved amino acids profile, and phenolic content (Servili et al. 2011). Fortification of milk with flavonoids rich *Cudrania tricuspidate* powder enhanced

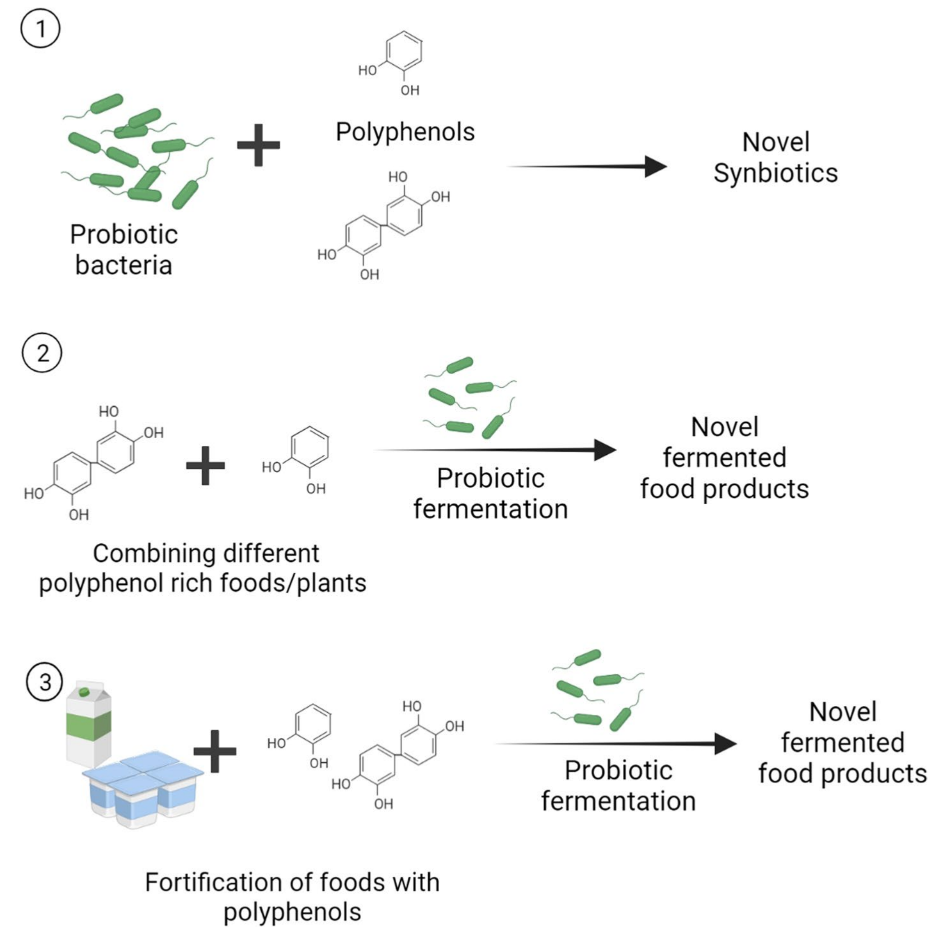


Fig. 4 Different strategies based on polyphenolic and probiotic amalgamation for the development of novel functional foods. *1.* Combinations of probiotic bacteria and polyphenols can act as synbiotics with improved functional response *2.* Different sources of polyphenols may be combined together and then fermented with specific probiotic bacteria that improves the overall phenolic profile of the combined food product while maintaining its probiotic viability *3.* Fortification of foods with polyphenols and their subsequent probiotic fermentation can also enhance their bioactive potential while still preserving the sensory experience in the novel functional food

the phenolic and flavonoid contents after fermentation and improved its antioxidant (DPPH radical and ABTS free radical cation scavenging) and antimutagenic activities (Lee et al. 2020). Similarly, green tea yoghurt, which is prepared by enrichment of traditional yoghurt with different varieties of tea is gaining popularity as a novel functional food (Amirdivani & Baba 2015). Recent studies have shown that green tea extracts can be successfully incorporated into yoghurt which induces the synthesis of new phenolic compounds, and enhance the antioxidant capacity while still maintaining the sensory quality and viability of beneficial microorganisms of raw yoghurt (Mediza Romero et al. 2021; Najgebaue-Lejko 2019; Rahmani et al. 2021; Shori et al. 2021; Świąder et al. 2020). Not only green tea, but fermentation with red ginger extract has also been demonstrated to enhance the bioactive potential of yoghurt without negatively affecting the growth of probiotic microorganisms (Larasati et al. 2018). A clinical study has further highlighted the applicability of a synbiotic yoghurt prepared by mixing probiotic bacteria, prebiotic oligosaccharides (2%), and pomegranate juice concentrate (20%) that resulted in improved systolic blood pressure and markers of blood cholesterol in mildly to moderately hypercholesterolemic and hypertensive subjects (Miremadi et al. 2017). A representative list of polyphenols-based novel functional foods prepared by selective fermentation with probiotic bacteria is presented in Table 2.

Conclusion

Several different food types have been fermented and commercialized, however, focus on fermented polyphenol-rich foods and their potential in the food industry is yet to gain its complete and deserving attention. This

Table 2 Representative examples of novel functional foods prepared by probiotic fermentation of polyphenols

S. no	Polyphenol or phenolic food source	Probiotic bacteria	Food type and characteristics	Reference
1	Green tea EGCG	*Lactobacillus fermentum*	Synbiotic food product with superior antioxidant and immunomodulatory activity	Sharma et al. 2019
2	*Cudrania tricuspidata* leaf extract	*Lactobacillus gasseri*	Synbiotic food prepared by addition of *Cudrania tricuspidata* extract to milk followed by fermentation; enhanced antioxidant capacity and production of novel metabolites	Oh et al. 2016
3	*Houttuynia cordata* leaf extract and green tea	*Lactobacillus paracasei* subsp. *paracasei*	Fermented product with increased levels of EGCG, EGCG, and chlorogenic acids, and superior anti-obesity effects *in vitro*	Wang et al. 2018
4	Mixture of vegetables and fruit juice	Lactic acid bacteria	Probiotic fruit-vegetable juice product with increased viability of probiotic bacteria and acceptable sensory score	Güney & Güngörmüşler 2021
5	*Cudrania tricuspidata* powder	*Streptococcus thermophilus, Lactobacillus paracasei*, and *Lactobacillus delbrueckii* subsp. *bulgaricus*	Fermented milk supplemented with *Cudrania tricuspidata* recorded low pH, improved lactic acid fermentation, and increased total phenolic and flavonoid contents	Lee et al. 2020

could be partly attributed to the traditional antimicrobial nature of polyphenols which, however, is being challenged in emerging studies as also discussed in this manuscript. The core principle of using polyphenolic fermented foods is related to their dual benefits, i.e., the ability of polyphenols to suppress various pathogens (while concurrently promoting probiotic growth) and the potency of probiotics to biotransform polyphenols during fermentation resulting in increased bioavailability and content of the native phenolic profile, that has immense potential for the development of novel functional food products. However, caution needs to be exercised since interactions between polyphenols and probiotic bacteria may not always be generalized but are likely to be dependent on the strain(s) of probiotic bacterial species as well as the type of polyphenol(s) used. Therefore, it is prudent to identify suitable combination(s) of probiotic bacteria and polyphenols relating to fermentability and possible health beneficial effects through *in vitro* and *in vivo* testing. Further, studies exploring combinations of polyphenols-rich medicinal plants for their fermentability with probiotic bacteria and potential transformation of native chemical profile and health benefits thereof are also lacking and should be pursued. To conclude, it is recommended that probiotic and polyphenolic amalgamation in foods be viewed within the purview of synergy as it represents an untapped research area that could potentially be an important source for the next generation of functional foods.

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RS conceived the idea, collected the data, wrote, and edited the manuscript. BD contributed to data collection and curation. BPS collected data and edited the manuscript. SK contributed to manuscript design and figures. All authors read and approved the final manuscript.

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Author details
[1]Faculty of Applied Sciences & Biotechnology, Shoolini University of Biotechnology and Management Sciences, Solan 173229, India. [2]Department of Microbiology, Central University of Haryana, Mahendragarh, India.

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