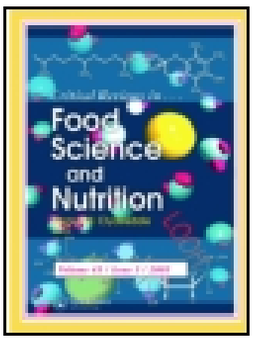

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Amalgamation of polyphenols and probiotics induce health promotion

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ABSTRACT

The residing microbiome with its vast repertoire of genes provide distinctive properties to the host by which they can degrade and utilise nutrients that otherwise pass the gastro-intestinal tract unchanged. The polyphenols in our diet have selective growth promoting effects which is of utmost importance as the state of good health has been linked to dominance of particular microbial genera. The polyphenols in native form might more skilfully exert anti-oxidative and anti-inflammatory properties but in a living system it is the microbial derivatives of polyphenol that play a key role in determining health outcome. This two way interaction has invoked great interest among researchers who have commenced several clinical surveys and numerous studies in in-vitro, simulated environment and living systems to find out in detail about the biomolecules involved in such interaction along with their subsequent physiological benefits. In this review, we have thoroughly discussed these studies to develop a fair idea on how the amalgamation of probiotics and polyphenol has an immense potential as an adjuvant therapeutic for disease prevention as well as treatment.

KEYWORDS

Probiotics; polyphenols; polyphenol catabolites; mutualistic relationship; therapeutic effects; dysbiosis; gut modulation

1. Introduction

The human body is an ecosystem in itself that harbours an overwhelming array of diverse species of microorganisms. The number of bacterial cells inhabiting the gut is ten times more than the total number of cells in our body, collectively making up to 100 trillion cells (Qin et al. 2010). Advanced metagenomic sequencing unveils that the genetic makeup of gut microbiota is at least 70–140 times larger than that of their host (Qin et al. 2010, Possemiers et al. 2011) encoding 10 million non-redundant genes (Li et al. 2014, Cani and Everard 2016). Consequently the combined genome of resident microbes bequeath the host with vital metabolic and physiological abilities that were otherwise not innate (Egert et al. 2006, Possemiers et al. 2011). The relative proportion of the 8 phylotypes that reside in human gut out of the 70 known bacterial divisions have been represented graphically in Figure 1 (Candela et al. 2010). This enormous genetic makeup of the residing microbiome equivalents it to a dynamic organ within the individual that holds a mammoth potential of influencing the health outcome of the host. Bäckhed et al. (2005), vehemently advocates that the gut microbes share a mutualistic relationship with the host as opposed to commensal, a term that implies that only one of the partner is benefited while the other remains ostensibly unaffected. This dynamic organ has an intricate interaction with all the nutrients that pass through the gastro-intestinal (GI) tract and dictates their final outcome. The "mutualistic co-evolution" of gut microbes and human host have programmed the former to derive energy from otherwise inaccessible nutrients while the host has adapted to recruit the novel end-products of microbial degradation. Although polyphenols are treated as non-nutrient xenobiotics with minimal bioavailability owing to their complex structures, they undergo extensive metabolism by the intestinal microbiota (Crozier, Jaganath, and Clifford 2009, Tuohy et al. 2012, Faria et al. 2014). The common ground between polyphenols and probiotics have been established by studies that claim polyphenols improve the microbial balance and in turn they metabolise polyphenols releasing derivatives that have a greater bioavailability.

Epidemiological studies have patronised the inverse relationship between polyphenol consumption and chronic diseases (Scalbert et al. 2005, Shahidi and Ambigaipalan 2015). Now here a question arises, is it the bioactivity of polyphenols alone or their interaction with the intestinal microbiota that is instrumental for promoting health? Studies have been conducted so far as to have a fair idea regarding the impact of polyphenol consumption on gut microbiota and vice-versa (Lee et al. 2006, Selma, Espín, and Tomás-Barberán 2009).

This is an evidence based review article where we will be summarizing the existing knowledge on the symbiotic impact of polyphenols and probiotics followed by how the two work together as a team affecting various physiological parameters.

2. Fate of ingested polyphenols

Polyphenols are a diverse group of secondary metabolites that are ubiquitously available in almost all plants (Santos-Buelga

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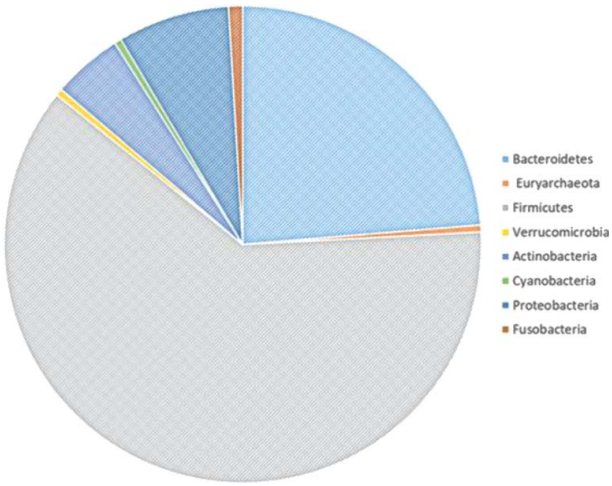


Figure 1. Relative proportion of the 8 phylotypes out of the 70 known bacterial divisions which have been found residing in the human gut microbiota. (Candela et al. 2010).

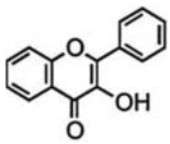
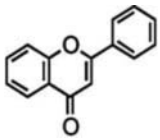
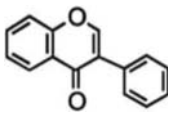
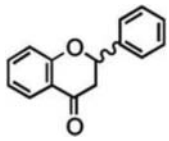
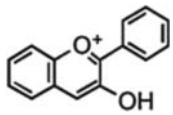
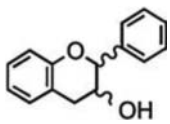
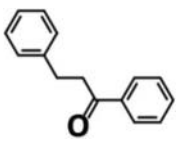
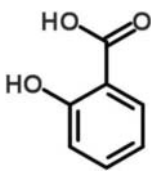
and Feliciano 2017). They can be accounted for the organoleptic properties such as the appealing colours, antimicrobial properties, protection against UV light and mild astringency of a particular plant product (Heleno et al. 2014). According to their heterogeneous chemical structure they can be classified into two main classes: flavonoids (that includes flavonols, flavanols, flavanones, flavones, anthocyanidins, chalcones, dihydrochalcones, dihydroflavonols and isoflavones) and non-flavonoids (that includes phenolic acids, lignans, and stilbenes) (Del Rio et al. 2013, Valdes et al. 2015). Table 1 shows the various types of naturally occurring polyphenols. In dietary components, polyphenols naturally occur in the following forms: free forms known as aglycones, glycosylated or acylated derivatives, polymers of varying chain length and different structures grouped together in so-called macromolecules (Erlund 2004, Eeckhaut et al. 2008, Perez-Jimenez et al. 2010).

We will be discussing next about the journey of a polyphenol moiety following ingestion. The mouth, which is the first site of digestion, contains saliva that plays a pivotal role in metabolism of polyphenols. Soon after ingestion, mastication increases the surface area of ingested food materials inevitably increasing the surface area for food-enzyme interaction (Chen 2014). Lipophilic polyphenols that are poorly soluble in water are capable of being solubilized either by whole saliva or also by salivary albumin and mucin thereby enhancing their bioavailability. Saliva can raise the retention of polyphenols for a longer period of time due to their ability to adhere to oral mucosal surfaces (Ismail, Sestili, and Akhtar 2012, Ginsburg et al. 2012). Moreover the salivary proline-rich proteins (PRPs) also have the ability to precipitate tanins by forming insoluble complexes, thus disrupting its bioavailability (Lu and Bennick 1998, Bennick 2002, Dinnella et al. 2009, McRae and Kennedy 2011).

The polyphenols pass through the stomach almost unchanged. Bermúdez-Soto, Tomás-Barberán, and García-Conesa (2007) carried out gastric-simulated digestion of chokeberry juice with pepsin–HCl (pH 2.0) for 2 hr and did not find a substantial detrimental effect on the levels of any of the major phenolic compounds in chokeberry juice. Additionally a slight increase (~7%; $p < 0.01$) in the quantities of total anthocyanins was detected after the gastric incubation (Bermúdez-Soto, Tomás-Barberán, and García-Conesa 2007). A lot of studies involving simulated digestion have accounted a notable increase in anthocyanin during gastric digestion (Tagliazucchi et al. 2010, Mosele et al. 2015, a). In the small intestine, the glycosylated polyphenols are cleaved to release their corresponding aglycones that can passively diffuse inside the epithelial cells. Deglycosylation of the glycosylated polyphenol moiety may take place by the action of lactase phlorizin hydrolase (LPH), a cellular membrane-bound protein present in the brush border of the epithelial cells. Owing to its occurrence LPH has the ability to hydrolyze flavonoid glycosides without transporting the glycosides into the cells (Day et al. 2000). Gee et al. (2000) demonstrated that when quercetin-3-glucoside and D-galactose are simultaneously present in the mucosal medium, the former inhibits intestinal transport of D-galactose. Furthermore it accelerates the efflux of labelled D-galactose from preloaded mucosal tissue as compared to a substrate-free medium. These observations from the above study put forward the possible interaction of the polyphenolic glucosides with the Na1-D-glucose or SGLT1 cotransporter. So another alternative step has been suggested in which the flavonoid glycoside is transported inside the epithelial cells aided by active sodium-dependent glucose transporter, SGLT-1 where it undergoes hydrolysis by a cytosolic β-glucosidase (CBG). Another study by Kottra and Daniel (2007) contradicts this finding and claims instead that transport currents of the human sodium-dependent glucose transporter (hSGLT1) do not transport any flavonoid glycosides (total 27 glucosides were used in the study). Furthermore flavonoids depending on their structure and position of substituents interact with the hSGLT1 and meticulously retard glucose absorption. However the authors did not suggest a potential alternative mechanism.

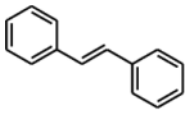
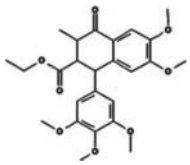
The resulting aglycones enter into the liver through the enterohepatic circulation and are subjected to Phase II metabolism. Here they undergo sulfation, glucuronation and/or methylation through the respective action of sulfotransferases (SULT), uridine-50-diphosphate glucuronosyltransferases (UGTs) and catechol-O-methyltransferases (COMT) (Wu, Cao, and Prior 2002). These conjugates then circulate in the blood albeit a major portion of these absorbed polyphenols are returned back to the small intestine via bile in sulphonated, gluconated and methylated forms. From here the conjugated polyphenols pass through and reach the colon. At this site, they can interact with microflora that possesses a spectacular armoury of enzymes that is capable of hydrolysing a huge assortment/category of substrates ranging from glycosides (like α-galactoside, β-glucoside, β-galactoside, rhamnoside), glucuronides, amides, esters, sulphates and lactones. They also carry out ring-cleavage, reduction, decarboxylation, demethylation, and dehydroxylation reactions (Selma, Espin, and Tomas-Barberan 2009, Chen and Sang 2014). Deglycosylation assisted by these microbial enzymes is the first step in glycosylated polyphenol metabolism (Németh et al. 2002, Braune and Blaut 2011, Serra et al. 2012). The conjugated moieties are cleaved by gut microflora and the resultant aglycones are subjected to ring fission, leading to the production of phenolic acids and hydroxycinnamates. Finally they are excreted from the body in the form of urine and faeces (van Duynhoven et al. 2011). The passage of

Table 1. Classification of Phenolic Compounds occurring in Food.

Classification of Phenolic Compounds occurring in Food				
Types		structure	common aglycones	common food sources
FLAVONOIDS	Flavonols		Kaempferol Quercetin Isorhamnetin Myricetin	apple, lingonberries, bilberries, and black currants yellow and red onions, garlic, broccoli, tea.
	Flavones		Apigenin Luteolin Wogonin Baicalein	celery, parsley, cereal grains.
	Isoflavones		Daidzein Genistein	soyabean, soy milk, tofu, legumes.
	Flavanones		Naringenin Hesperetin	oranges, grapefruit, other citrus fruits.
	Anthocyanidins		Pelargonidin Cyanidin Delphinidin Peonidin Petunidin Malvidin	blueberry, elderberries, blackcurrant, grapes, cherries, wine.
	Flavan-3-ols		Epicatechin Catechin Proanthocyanidins	green tea, black tea, chocolate, wine, apple.
	Dihydrochalcones		Phloridzin Aspalathin	apple, rooibos tea.
NON-FLAVONOIDS	Phenolic acids		Nothofagin Gallic acid Ferulic acid Ellagic acid Caffeic acid	raspberries, strawberries, blackberries, pomegranate, walnuts, hazelnuts, wine, coffee, maize, flaxseed, chicory, olive.

(*Continued on next page*)

Table 1. (*Continued*).

Classification of Phenolic Compounds occurring in Food			
Types	structure	common aglycones	common food sources
Stilbene		Resveratrol Pterostilbene Piceatannol	red wine, white wine, red grapes, black grapes, green grapes, fox grapes, cranberry, strawberry, bilberry, blueberry, lignoberry, redcurrant.
Lignans		Secoisolariciresinol Matairesinol Medioresinol Pinoresinol Lariciresinol	Sesame seed, flaxseed, sunflower seed, bread, oat whole grain flour, buckwheat whole grain flour, rye whole grain flour, olive oil.

dietary polyphenols and their metabolites through the GI tract has been illustrated in Figure 2 (Cardona et al. 2013). Enzymatic activity increases polyphenol content by releasing them from the plant matrix (Shim et al. 2012, Gawlik-Dziki 2012).

The occurrence of a wide range of phenolic acids and other related simplified compounds in urine and circulating plasma, significantly different from native polyphenols has been validated in multitude of studies (González-Barrio, Edwards, and Crozier 2011, Aura et al. 2012, Espín et al. 2013, Ferrars et al. 2014, McKay et al. 2015, Del Pino-García et al. 2016). Muniandy, Shori, and Baba (2015) in their study observed that several phenolic compounds that were initially present in tea water extracts could not be traced by LCMS analysis in yoghurt fortified with tea extracts. Moreover newer phenolic compounds were identified in those tea polyphenol fortified yogurts. Chromatographic analysis of faeces collected from animal and human subjects fed with polyphenols have also yielded similar results (Li et al. 2015, Cui et al. 2016). Recovery of polyphenols from the urine and faeces of study subjects (either animals or human) consuming virgin olive oil, thyme, grape seed proanthocyanidins (Choy et al. 2014), coffee (Marmet et al. 2014), green tea (Vetrani et al. 2016), cranberry (Feliciano et al. 2016, Peron et al. 2017), grape pomace (Sasot et al. 2017), orange juice (Pereira-Caro et al. 2016), strawberry (Sandhu et al. 2018) revealed new components somewhat different from the original constituents of the aforementioned food items confirming a plausible bio-degradation and biotransformation during the transit period (Rothwell et al. 2016). Table 2 summarizes the polyphenolic catabolites obtained due to microbial degradation of common polyphenol rich foods. Dall'Asta et al. (2012) employed an in-vitro faecal fermentation model to detect the major metabolites produced from 16 polyphenol-rich foods and identified twenty four phenolic metabolites using high-performance liquid chromatography coupled with tandem mass spectrometry. In a randomized, crossover, controlled interventional trial, the individuals who had increased faecal concentration of Bifidobacterium due to consumption of red wine were found to have higher urinary concentration of anthocyanin metabolites as well (Boto-Ordóñez et al. 2014). Furthermore when antibiotics were provided prior to polyphenol feed to the animals and human subjects, urinary analysis revealed lower recovery of certain polyphenolic metabolites in comparison to those who weren't dosed with antibiotics (Orrego-Lagarón et al. 2015). The accumulated evidence reflecting disparity in the type of polyphenols naturally occurring in food stuffs and those circulating in blood and urine suggests the omnipotent role of microbial consortia in biodegradation of parent polyphenols into simpler products.

Few pharmacokinetic studies deduce that phenolic ring fission products appear in significant amounts after 4 hr in plasma and between 8 to 12 hr in urine following ingestion of polyphenols (Lee et al. 2002, Del et al. 2010, Pimpao et al. 2015). Recently in 2016, Xie et al. conducted a pharmacokinetic trial on 6 adults to ascertain the bioavailability of polyphenol metabolites following consumption of aronia berry extract. In spite of considerable inter-individual variation in pharmacokinetic parameters, the polyphenol catabolites appeared in plasma and urine between 1.0 to 6.33 hr.

Variation in absorption is also subject to the position of glycosylation. Angelino et al. (2013) compared the bioavailability of apigenin and its glycoside, apigenin 8-C-glucoside-2-O-xyloside using a rat model and illustrated for the first time that the flavone-C-glycosides could be absorbed unchanged as opposed to its O-glycoside analogue. 40 mins after its consumption, apigenin was found as aglycone and apigenin-glucuronide form in enterohepatic circulation whilst apigenin 8-C-glucoside-2-O-xyloside remained almost unchanged.

These results open up a possibility for supplementing probiotic bacteria to individuals who are 'low polyphenol-fermenting metabotype' to increase their colonic microbial capacities of metabolizing dietary polyphenols (Barroso et al. 2014) as all the ingested polyphenols will ultimately interact with the gut microbiota. Although inter-individual variations concerning the metabolism of certain polyphenols is an important determinant of effectivity involving such supplementation. For instance, Bode et al. (2013) identified

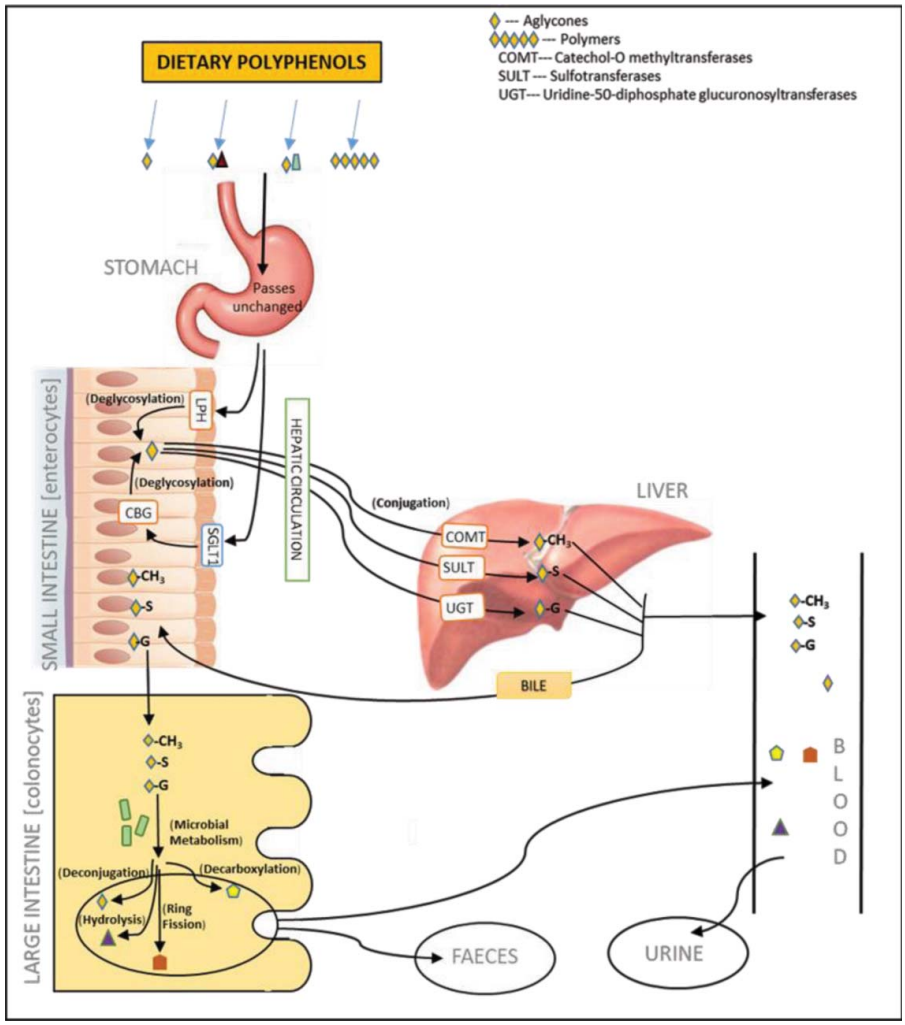


Figure 2. Routes for dietary polyphenols and their metabolites in humans. Within the host, dietary polyphenols and their microbial metabolites successively undergo Phase I and II metabolism in the intestine and liver respectively, the conjugated polyphenols then are degraded by the bacteria residing in the gut, the absorbed polyphenols enter into the systemic circulation, finally eliminated from the body through urine and faeces. (Cardona et al. 2013).

two bacterial trans-resveratrol metabolites both in vitro and in vivo: 3,4′-dihydroxy-trans-stilbene and 3,4′-dihydroxybibenzyl, that were previously unknown. However the formation of these metabolites varied among the volunteers.

3. Polyphenols and probiotic viability

Natural selection at two levels has been crucial in sculpting the configuration of the microbial contents of intestine. Firstly, at the microbial level, several physical, environmental and lifestyle factors govern the 'fitness' of specific bacterial species, selecting them for survival. Secondly, at the host level, the unsatisfactory performance of resident bacteria affect the 'fitness' of host adversely (Bäckhed et al. 2005). The genetic makeup of the gut microbiota is a vital determinant of health. The resident bacterial species not only govern the metabolic activities and immunological responses but are also linked to cognition and fundamental behaviour patterns (Murri et al. 2013, Tilg and Moschen 2014, Dinan, Borre, and Cryan 2014). Newer techniques have been established to discern the species that frequently occur in the gut of healthy individuals and a pattern has been obtained. Desirable modulation of the gut microbiota is a strategy that can be implemented to develop a new therapeutic approach in order to attain good health (McLean et al. 2015, Anhê et al. 2016). Long term dietary intervention has profound impact in altering the microbiota composition (Conlon and Bird 2014, Moloney et al. 2016) and can be employed as the practical methodology for accomplishment of this pursuit. Numerous studies have refuted that polyphenols have prebiotic effect (Valdes et al. 2015) i.e. they selectively promote the growth and adhesion of probiotic bacteria. This fact is of considerable importance as not all plant extracts that are capable of inhibiting pathogenic bacteria can promote growth of probiotic bacteria as well (Yang et al. 2012).

3.1. Polyphenol probiotic interaction in in-vitro condition

Various in-vitro studies have been carried out to assess the relationship between polyphenols and viability of probiotic bacteria. Reports have shown that polyphenol extracts in native form (Khalil et al. 2010, Mazzeo et al. 2015) or from different sources like flowers (China et al. 2012), grape seed (Cueva et al. 2013), honey (Das et al. 2015), pear (Sarkar et al. 2015) and red coloured fruits (Coman et al. 2017)

Table 2. Polyphenolic catabolites obtained from some polyphenol rich foods.

Name of food item	Native polyphenols present	Polyphenolic catabolites obtained from some polyphenol rich foods	Reference
BLACKBERRY	pelargonidin hexoside, cyanidin hexoside, cyanidin malonylhexoside, cyanidin dioxaloylhexoside, cyanidin rutinoside, coumaroylhexoside, caffeoylhexoside, quercetin hexoside, quercetin glucuronide, isorhamnetin glucuronide, salicylic acid.	cyanidin-3-O-glucoside, cyanidin-O-glucuronide, peonidin-O-glucuronide. cyanidin 3-O-glucoside. protocatechuic acid	(Felgines et al. 2005) (Perez-Jimenez et al. 2010) (Dall'Asta et al. 2012)
RASPBERRIES	pelargonidin hexoside, cyanidin hexoside, pelargonidin rutinoside, coumaroyl hexosides, caffeoyl hexosides, hydroxybenzoic acid, salicylic acid.	4-hydroxybenzoic acid, 4-hydroxymandelic acid, 3-methoxy-4-hydroxymandelic acid, 3,4-dihydroxyphenylacetic acid, 4-hydroxyphenylacetic acid 3-(3-hydroxyphenyl)hydracrylic acid, 3-(4-hydroxyphenyl)lactic acid, 3-methoxy-4-hydroxyphenylacetic acid, 4-hydroxyhippuric acid, hippuric acid. protocatechuic acid, benzoic acid.	(Gonzalez-Barrio, Edwards, and Crozier 2011) (Dall'Asta et al. 2012)
STRAWBERRIES	pelargonidin hexoside, cyanidin hexoside, pelargonidin rutinoside, coumaroyl hexosides, caffeoyl hexosides, hydroxybenzoic acid, salicylic acid.	pelargonidin 3-O-glucoside, urolithin B. gallic acid, quinic acid.	(Perez-Jimenez et al. 2010) (Dall'Asta et al. 2012)
BLUEBERRY	cyanidin pentoside, delphinidin pentoside, cyanidin hexoside, delphinidin hexoside, petunidin hexoside, malvidin hexoside, peonidin hexoside, catechin, epicatechin, coumaroylhexosides, coumaroylquinic acids, caffeoylhexosides, caffeylquinic acids, feruloyl hexosides, feruloylquinic acids, sinapic acid, hexosides, procyanidin dimers b-type, salicylic acid.	cyanidin 3-O-glucoside, cyanidin 3-(caffeoyl)(p-coumaroyl)diglucoside-5-glucoside, cyanidin 3-(feruloyl)diglucoside-5-glucoside, cyanidin 3-(glycopyranosyl-sinapoyl)diglucoside-5-glucoside, cyanidin 3-(p-coumaroyl)(sinapoyl) triglucoside-5-glucoside, cyanidin 3-(p-coumaroyl)diglucoside-5-glucoside, cyanidin 3-(sinapoyl)diglucoside-5-glucoside, cyanidin 3,5-diglucoside, cyanidin 3-diglucoside-5-glucoside, cyanidin 3-O-arabinoside, cyanidin 3-O-galactoside, cyanidin 3-O-glucoside, cyanidin 3-O-glucosylrutinoside, cyanidin 3-O-rutinoside, cyanidin 3-O-sambubioside, cyanidin 3-O-sophoroside, cyanidin 3-O-xilosylrutinoside, delphinidin 3-O-arabinoside, delphinidin 3-O-galactoside, delphinidin 3-O-glucoside, delphinidin 3-O-rutinoside, delphinidin 3-O-sambubioside, malvidin 3-O-arabinoside, malvidin 3-O-galactoside, malvidin 3-O-glucoside, petunidin 3-O-arabinoside, petunidin 3-O-galactoside, petunidin 3-O-glucoside. gallic acid, coumaric acid, protocatechuic acid, quinic acid, dihydrocaffeic acid, hydroxyl benzoic acid.	(Perez-Jimenez et al. 2010) (Dall'Asta et al. 2012)
APPLE	caffeic acid, catechin, epicatechin, coumaroylquinic acids, caffeoylquinic acids, phloretin hexoside, quercetin rhamnoside, quercetin hexosides, phloretin xylosyl hexoside, procyanidin dimers b-type, procyanidin trimers b type, procyanidin tetramers b-type.	caffeic acid, catechin, epicatechin, coumaroylquinic acids, caffeoylquinic acids, phloretin hexoside, quercetin rhamnoside. quercetin hexosides, phloretin xylosyl hexoside, procyanidin dimers b-type, procyanidin trimers b type, procyanidin tetramers b-type.	(Dall'Asta et al. 2012)
BLACKCURRANT	delphinidin-3-rutinoside, delphinidin-3-glucoside, cyanidin-3-rutinoside, cyanidin-3-glucoside, myricetin, quercetin, kaempferol, isorhamnetin, myricetin glycosides, quercetin glycosides, kaempferol glycosides, isorhamnetin glycosides.	3-(4′-hydroxy-phenyl) propionic acid glucuronide, 4-hydroxy-benzoic acid glucuronide, 3-methoxy-4-hydroxy-phenylacetic glucuronide, 2-(3′- and 4′-hydroxyphenyl) acetic glucuronide, hippuric acid glucuronide. cyanidin 3-O-glucoside, hesperidin, hesperidin 7-O-glucoside, naringin, narirutin. dihydroferulic acid, sinapic acid, protocatechuic acid.	(Perez-Jimenez et al. 2010) (Vallejo et al. 2010) (Dall'Asta et al. 2012)
ORANGE	delphinidin hexoside, cyanidin malonyl hexoside, cyanidin dioxaloyl hexoside, cyanidin hexoside, cyanidin sophoroside, delphinidin rutinoside, coumaroyl hexoside, feruloyl hexoside, sinapic acid hexoside, kaempferol hexoside, narirutin, didymin, eriocitrin, diosmin, hesperidin, hesperetin-7-O-rutinoside.	3-(4′-hydroxy-phenyl) propionic acid glucuronide, 4-hydroxy-benzoic acid glucuronide, 3-methoxy-4-hydroxy-phenylacetic glucuronide, 2-(3′- and 4′-hydroxyphenyl) acetic glucuronide, hippuric acid glucuronide. cyanidin 3-O-glucoside, hesperidin, hesperidin 7-O-glucoside, naringin, narirutin. dihydroferulic acid, sinapic acid, protocatechuic acid.	(Perez-Jimenez et al. 2010) (Vallejo et al. 2010) (Dall'Asta et al. 2012)

(*Continued on next page*)

Table 2. (*Continued*).

Name of food item	Native polyphenols present	Polyphenolic catabolites obtained from some polyphenol rich foods	Reference
POMEGRANATE	pelargonidin hexoside, cyanidin hexoside, delphinidin hexoside, cyanidin dihexoside, delphinidin dihexoside, gallic acid, ellagic acid, ellagic acid pentoside, ellagic acid rhamnoside, ellagic acid acetylpentoside, galloylhexahydroxydiphenoyl-hexose, punicalin, punicalagin a, punicalagin b	urolithin A, urolithin A-3-O-glucuronide, urolithin B, methylated urolithin B, urolithin A-3-O-glucuronide, urolithin B-3-O-glucuronide, 3,8-O-dimethylellagic acid-2-O-glucuronide. gallic acid, pyrogallol, phlorogucinol, syringic acid, protocatechuic acid.	(Seeram, Henning and Zhang 2006) (Dall'Asta et al. 2012)
TEA	gallic acid, catechin, epicatechin, gallocatechin, epigallocatechin, coumaroylquinic acids, galloylquinic acid, caffeoylquinic acids, catechin gallate, epicatechin gallate, kaempferol hexosides, gallocatechin gallate, epigallocatechin gallate, quercetin hexosides, theaflavin, procyanidin dimers b type, kaempferol rutinoside, prodelphinidin dimers b-type, rutin, theaflavin gallate, theaflavin digallate, quercetin-rhamnose-hexose-rhamnose.	2-(3′-hydroxyphenyl) acetic acid, 2,6-dihydroxybenzoic acid, 1,2,3 trihydroxyphenol, 3-phenylpropionic acid, 5-(3′,4′-dihydroxyphenyl)-γ –valerolactone. phlorogucinol, pyrogallol, coumaric acid, gallic acid, 5-(30,40-dihydroxyphenyl)-γ-valerolactone, 5-(30,40,50-trihydroxyphenyl)-γ-valerolactone, 5-(30-hydroxyphenyl)-γ-valerolactone, protocatechuic acid, dihydrocaffeic acid, homovanillic acid, quinic acid.	(Gross et al. 2010) (Dall'Asta et al. 2012)
RED WINE	citric acid, gallic acid, resveratrol-hexoside, kaempferol-hexoside, laricitrin-hexoside, myricetin-hexoside, quercetin-hexoside, quercetin-glucuronide, syringetin-hexoside, epicatechin, catechin, gallocatechin, peonidin-hexoside, peonidin-3-O-(C6-coumaroyl)-hexoside, petunidin-3-acetylhexoside, petunidin-hexoside, petunidin-3-(6-O-coumaroyl)-hexoside, delphinidin-hexoside, delphinidin-glucuronide, delphinidin-3-acetylhexoside, cyanidin-hexoside, cyanidin-6-O-coumaroylhexoside, malvidin-hexoside, malvinidin-3-acetylhexoside, malvidin-3-coumaroylhexoside, malvidin-3-hexosylacetaldehyde, malvidin-3-hexosylpiruvate, malvidin-3-O-coumaroylglucoside pyruvate, malvidin-3-O-glucosyl-8-ethyl-epicatechin, carboxypyrano-malvidin-3 coumaroylglucoside.	malvidin 3-O-arabinoside, malvidin 3-O-galactoside, malvidin 3-O-glucoside, petunidin 3-O-arabinoside, petunidin 3-O-galactoside, petunidin 3-O-glucoside. 3-(3′-hydroxyphenyl) propionic acid, 2-(3′-hydroxyphenyl) acetic acid, 3,5-dimethoxy-4-hydroxybenzoic acid, 3-hydroxyhippuric acid, hippuric acid, 2-(4′-hydroxyphenyl) acetic acid. 3-(3′-hydroxyphenyl) propionic acid, 2-(4′-hydroxyphenyl) acetic acid, 3-(3′,4′-dihydroxyphenyl) propionic acid, 3-(4′-hydroxyphenyl) propionic acid, 5-(3′,4′-dihydroxyphenyl)-γ –valerolactone, γ –valerolactone. 3-(3′,4′-dihydroxyphenyl) propionic acid, 2-(3′,4′-dihydroxyphenyl) acetic acid, 5-(3′-hydroxyphenyl) pentanoic acid, 3,5-dimethoxy-4-hydroxybenzoic acid, 3 methoxy-4-hydroxybenzoic acid.	(Perez-Jimenez et al. 2010) (Jacobs et al. 2012) (Sanchez-Patan et al. 2012) (Aura et al. 2012)
CHOCOLATE	epicatechin, catechin, procyanidin dimers b-type, procyanidin trimers b-type, procyanidin tetramer b-type.	3-(3′-hydroxyphenyl) propionic acid 5-(3′,4′-dihydroxyphenyl) valerolactone and conjugates 5-(3′,4′-dihydroxyphenyl) valerate conjugates 4-hydroxy-5-(3′,4′-dihydroxyphenyl) valeric acid phenylvalerolactone derivatives. O-methyl-(epi)catechin–sulphate, (epi)catechin-O-sulphate 3-(3′-hydroxyphenyl) propionic acid, 2-(3′-hydroxyphenyl) acetic acid, 3,4-dihydroxybenzoic acid. 5-(30,40-dihydroxyphenyl)-γ-valerolactone, (3,4-dihydroxyphenyl)acetic acid, protocatechuic acid, hydroxybenzoic acid, salicylic acid.	(Llorach et al. 2009) (Mullen et al. 2009) (Fogliano et al. 2011) (Dall'Asta et al. 2012)
SOY	kaempferol-3-O-α-L-rhamnopyranosyl, β-D-glucopyranosyl, β-D-galactopyranoside, kaempferol-3-O-(2,6-di-O-R-rhamnopyranosyl) β-galactopyranoside, kaempferol-3-O-digalactopyranoside, kaempferol-3-O-diglucopyranoside, kaempferol-3-O-rutinoside, genistein-7-O-glucoside, genistein-malonylglycoside, genistein-7-O-malonylglucoside, genistein-acetylglycoside, daidzein-7-O-glucoside, daidzein-7-O-malonylglucoside, coumestrol-7-O-glucoside.	2-(3′-methoxy–4′-hydroxyphenyl) acetic acid, 2-(4′-hydroxyphenyl) acetic acid. O-demethylangolensin, equol. O-demethylangolensin, equol, dihydrogenistein, glycitein	(Gao et al. 2006) (Possemiers et al. 2008) (Perez-Jimenez et al. 2010)

have exhibited antimicrobial effects against pathogens but growth promoting effects on probiotics. In 2008, Parkar, Stevenson, and Skinner investigated the effect of polyphenols at doses likely to be present in the gut on growth and adhesion of few species of probiotic and pathogenic bacteria and found that the gram-positive enteropathogen *Staphylococcus aureus* was most sensitive to the inhibitory effect of polyphenols followed by the gram-negative pathogen *Staphylococcus typhimurium* whereas probiotic bacteria *Lactobacillus rhamnosus* was less sensitive to the polyphenols and required a minimum inhibitory concentration of at least 125 μg/ml. Similar effects were observed while

ascertaining the adhesive properties of different bacterial species. At doses of 30 μg/ml all the polyphenols demonstrated an inhibitory effect on the adhesion of the pathogenic strain *S. typhimurium* but had little inhibitory effect on the adhesion of *lactobacilli* to Caco-2 cells. Moreover pre-treatment of Caco-2 cells with the polyphenols phloridzin and rutin (at concentration 30 and 100 μg/ml respectively) lead to an incredible hike in the adhesive properties of *Lactobacilli* under both aerobic and anaerobic conditions (Shinde et al. 2014). In another study pre-treatment of the cell free supernatant of Lactobacillus casei with 3% cocoa powder seemed to intensify its antimicrobial and adhesive properties although the authors haven't drawn any conclusion regarding the minimum effective dosage (Peng, Reichmann, and Biswas 2015).

Incubation of probiotic bacteria with polyphenolic compounds not only enhance viability but also seem to improve other characteristic features such as short chain fatty acid (SCFA) production. Parkar, Trower, and Stevenson (2013) quantified the SCFA production among Bifidobacterium species and observed significantly higher production than that of the controls. The highest amount reported was 73.7 μmol/mL which resulted from incubation with caffeic acid at 10 μg/mL concentration although increase in concentration of polyphenols did not have any augmenting effect on the yield of SCFA. Zhang et al. (2013) too observed selective growth promoting effects of abundantly occurring tea catechins—epigallocatechin gallate, gallocatechin gallate and O-methylated form of epigallocatechin gallate acquired from oolong tea samples on Lactobacillus and Bifidobacterium species along with remarkable increase in generation of SCFA. In another study grape extracts inoculated with faeces collected from healthy individuals abstaining from antibiotic therapy for the past 6 months were incubated for 48 hours and samples were collected at intervals of 0, 5, 10, 24, 30 and 48 hours to assess the changes in bacterial population (using Fluorescence in situ hybridization, FISH). Except for an increase in the Lactobacillus population at first stages of fermentation (5–10 hr) no other significant changes were observed in the microflora species (Cueva et al. 2013).

This raise in viability is a desirable quality in food products packaged under the category of 'probiotic foods'. Various attempts have been made to appraise the sustainability of this interaction between polyphenols and probiotics during food processing and storage. Shinde, Sun-Waterhouse, and Brooks (2014) concluded from their study that co-encapsulation of *L.acidophillus* with apple skin polyphenol extracts and alginate significantly reduced cell loss after 50 days at both low temperature and acidic pH as compared to encapsulation with alginate alone and un-encapsulated probiotics. The team carried out another study (Shinde, Brooks, and Sun-Waterhouse 2015) to determine the viability of probiotic bacteria *L.acidophilus* in skimmed milk spiked with polyphenols extracted from apple (at 1 and 2% w/v). Polyphenol spiked milk had considerably greater count of probiotic bacteria compared to control milk containing no added polyphenols thereby improving the shelf life of the probiotic enriched food product. Polyphenols added separately (at 1% w/v) to skim milk were also found to increase viability of L. acidophilus in the following order: p-coumaric < quercetin < chlorogenic acid < phlorizin < epicatechin < rutin. Other experiments comprising incubation or encapsulation of probiotic bacteria with polyphenol rich formulations of green, black and white tea (Muniandy, Shori, and Baba 2015), Thai herbal extracts (Chaikham 2015) authenticate the rise in viability of probiotic cell counts and surface characteristics during the entire period of storage in harsh environmental conditions. In another study onion juice with its consortium of polyphenols, soluble dietary fibre, vitamins and minerals stimulated the growth and acidification of the bacterial strain *L. acidophilus* appreciably (Li et al. 2016). Various studies employed to prepare fermented milk by using tea extracts (Zhao and Shah 2014, Li et al. 2016), olive polyphenols (Georgakouli et al. 2016) and grape pomace extract (Dos Santos et al. 2017), along with probiotic bacteria assisted in estimating the viability of bacteria in fermented milk at different intervals. It was observed that the addition of polyphenol extract in fermented milk resulted in significant increase in the growth and viability of probiotic bacteria over a longer duration, maintaining the minimum viability required to be considered as a probiotic product which is at least 8–9 log CFU of probiotic microorganism per serving portion (1 cup or 200 mL for fermented milks). Moreover the polyphenolic extracts did not inhibit the starter culture or the activity and growth of probiotic microorganisms in fermented milk but limited the growth of yeasts and moulds. Polyphenols extracted from other common sources were also found to be effective in boosting probiotic growth and viability. Recently de Llano et al. (2017) reported no significant increase in polyphenol concentration on incubation of wine polyphenols with probiotic strains except for *L.plantarum* CLC 17, where the total polyphenol concentration increased up to 132.22% after 24 hour incubation.

3.2. Gastrointestinal Simulation models predicting growth of probiotics in presence of polyphenols

Duque et al. (2016) carried out a simulated digestion mimicking the colon environment in SHIME Model to analyse the interaction of orange juice and gut microbiota obtained from the faecal sample of a healthy individual. The study reported that orange juice increased the bacterial populations of *Lactobacillus* and *Bifidobacterium* by 1 log CFU at the same time caused 1 log CFU reduction in bacteroide populations. Another study involving simulation of the colon environment by Kemperman et al. (2013) dealt with the effects of black tea and red wine polyphenols on the gut microbiota profiles. After incubation of 8 weeks, qPCR results indicated considerable antimicrobial effects along with reduction at a range varying between 1 and 2 log units. *Bifidobacteria* appeared to be most inhibited whereas bacteroides remained least affected. No significant stimulatory effect of the polyphenols on the targeted bacterial species had been observed in this study. So it may be

concluded that the polyphenol degrading enzyme activities of probiotic bacteria are strain dependent.

3.3. Interaction of polyphenols with probiotics in living systems

Controlled, randomised, crossover intervention studies that involved oral administration of polyphenols from different sources like dates (Eid et al. 2015), wine (Moreno-Indias et al. 2016), could elevate the cell count of probiotic bacteria- *Lactobacillus* and *Bifidobacterium* in faeces. Jang et al. (2016) fed cocoa to pigs, followed by microbial analysis of stool samples to detect the hike in growth of desirable bacteria. The abundance of *Lactobacillus* and *Bifidobacterium* species in the faeces increased by 7-fold and 9-fold respectively in pigs fed with 20 gm coco powder each day in comparison to the unsupplemented groups. On analysing the microbial composition of stools of cocoa husk fed pigs by fluorescence in situ hybridization, a decrease of Firmicutes and an increase of Bacteroidetes was detected (Magistrelli et al. 2016). This finding indicates the prebiotic effect of cocoa husks but cocoa husks are a miscellany of fibre and polyphenols therefore the discrete role of its polyphenol contents could not be delineated. Guglielmetti et al. (2013) reported consumption of wild blueberry drink could increase the cell concentration of various *Bifidobacterium* strains in particular *B. longum* subsp. *infantis* which was otherwise absent in faeces of healthy subjects enrolled in the study before the wild blueberry drink treatment. Thus the aforementioned studies indicate that viability of *Lactobacilli* and *Bifidobacterium* may be relatively unaffected and/or stimulated in the gut by polyphenols.

It has been monitored that probiotic bacteria are capable of growing in a medium consisting polyphenols possibly because they can utilise these compounds as substrates to derive energy (Hervert-Hernández et al. 2009). de Lacey et al. (2014b) observed the capability of *Bifidobacterium animalis* B94 to survive in media containing only polyphenols like epigallocatechin, catechin, epicatechin, epicatechin-3-gallate, quercetin-3-O-galactoside, quercetin-3-O-glucoside, kaempferol-3-O-rutinoside, kaempferol-3-O-glucoside as the sole source of carbon. The glycosylated flavonoids were observed to prolong survival of *B. animalis* B94 for at least 48 hours of incubation. However the greatest reduction in the number of viable cells was detected in the solution comprising kaempferol-3-O-rutinoside, a polyphenol that possesses rhamnose in its structure because *B. animalis* B94 bacterium is more efficient in hydrolysing galactosidic and glucosidic bonds in comparison to rhamnosidic bonds (de Lacey et al. 2014a). Previously the authors had analysed the enzymatic activities of β-glucosidase, β-galactosidase and α-rhamnosidase in various probiotic strains and observed that most of the strains registered the lowest activities with α-rhamnosidase.

The propensity of glycosylated flavonoids to prolong viability of probiotic bacteria lies to the latters' prodigious assemblage of glycosidic enzymes (Nemeth et al. 2003). Only 98 glycoside hydrolases have been reckoned so far that are encrypted by the 2.85-Gb genome present in the human body. On the other hand the collective genome of the resident microbial troupe endow the host with ability to synthesise biomolecules dedicated to recognition, binding, metabolism and transport of specific carbohydrates encountered in the host system. The aggregate of gut symbionts consists a sum total of 156 carbohydrate-active enzymes (CAZymes) which is inclusive of 77 glycosidase, 35 glycosyltransferase, 11 carbohydrate-esterase, 12 polysaccharide lyase and 21 carbohydrate-binding moiety (Turnbaugh et al. 2009, Candela et al. 2010). They form a glycobiome that can degrade polysaccharides like-pectin, xylan, hemicellulose and arabinose that the host by itself is incapable of metabolising due to deficiency of the essential enzymes (Bäckhed et al. 2005). Genetic analyses of three gut Bacteroides: *B. distasonis B. thetaiotaomicron* and *B. vulgatus* by Xu et al. (2003, 2007) provide remarkable insight on the carbohydrate foraging activities in comparison to non-resident microbes. *B. thetaiotaomicron* contain a repertoire of glycoside hydrolases that can metabolise a variety of plant and host glycans. Although *B. distasonis* lacks several polysaccharidases it renders the two carbohydrate-processing enzymes, α-amylase-related proteins and N-acetylhexosaminidases surpassing other gut Bacteroidetes. Lastly, *B. vulgatus* has the most consummate set of enzymes that can degrade even pectin. In a similar study involving analyses of functional genomics of the two very popular probiotic genera *Bifidobacterium* and *Lactobacillus*, were reported to possess 30% higher genes responsible for carbohydrate metabolism with respect to that of other resident bacteria, *Escherichia coli*, and the non-gut bacteria *Lactococcus lactis*. Kelly et al. (2016), isolated 13 different types of α-glucosidases from *Bifidobacterium* strains that can act on a melange of α-glucosidic linkages facilitating their survival in competitive gut environment. Very recently Do, Zafar and Saier Jr. (2017) screened the genomic sequence of few probiotic and pathogenic strains to identify the transport proteins constituted by them. The team of authors found that the probiotic bacteria had transport proteins specific for nutrients ubiquitous to the extracellular environment (raffinose, maltose, cellobiose, etc.). On the other hand the pathogenic strains encoded for transport proteins that were compatible to the nutrients occurring in the cell cytoplasm (glucose, fructose, phosphoglycerate, di- and tricarboxylates, etc.). Hence, this attribute facilitates the probiotic strains to utilise the resultant polyphenolic catabolites obtained following disintegration.

Glycosidase enzyme activity assays have been carried out on probiotic strains isolated from various sources to assess the type and extent of enzymatic activity. Landete et al. (2014) pointed that the β-glucosidase activity of *L. plantarum* could be related with the widespread presence on Lp_3629 protein. Bacterial enzyme activity, the reliable indicator of microbial viability and is susceptible to the polyphenol concentration. The activity of microbial enzymes in the gut remained un-inhibited on supplementing ellagitannin to turkeys (Juskiewicz et al. 2015) although an inhibitory effect was observed in another experiment where rats were fed with diet containing a higher amount of ellagitannins (Fotschki et al. 2014). The concentration of polyphenol is crucial as at low to moderate concentrations they promote growth of probiotic species whereas at high

concentrations they can suppress their growth (Negi and Jayaprakasha 2001, Fotschki et al. 2014).

In vivo assessment carried out by Zduńczyk, Juśkiewicz, and Estrella, (2006) reported that flavonoid extracts singly could decrease the activity of bacterial β-glucosidase and α-and β-galactosidases in the caecal digesta. In contrast, addition of the flavonoid extract to inulin-containing diets augmented the activity of α-glucosidase, α-galactosidase, and β-galactosidase. Zduńczyk, Juśkiewicz, and Estrella, (2006) had previously concluded from their in-vivo study that the effect of polyphenol extract was less pronounced than inulin in improving the weight of caecal content. In another more recent study by Neyrinck et al. (2013) pomegranate peel extract given to rats along with high fat diet led to a remarkable increase in the weight of caecal content as well as the caecal pool of Bifidobacterium as compared to mice feeding on high fat diet only. Therefore synonymous intake of polyphenols and soluble dietary fibre is suggested for optimal functioning of the two food components (Fotschki et al. 2014, 2016, Jurgoński et al. 2015).

4. Native polyphenols or polyphenolic catabolites?

Previously it was believed that metabolism of polyphenols by GI enzymes may be responsible for impeding their bioactivity but now with advancement in studies the beneficiary effect of polyphenol rich food has been attributed to the products of degradation. The association between products of colonic metabolism and ingested polyphenols have already been established (Clifford, van der Hooft, and Crozier 2013, Vetrani et al. 2014, Vetrani et al. 2016, Zamora-Ros et al. 2016). The beneficial effects of polyphenols following oral ingestion can be exerted only if these xenobiotic molecules after being released from food matrices pass through the intestinal barrier ultimately to be transported by blood from the absorption site to target tissues and organs. It is very unlikely for the ingested polyphenol to reach the target tissue, rather simpler metabolites following extensive degradation will be transported in plasma. So basically metabolism is the indispensable phenomenon that induces bioavailability and bioactivity (Gonthier et al. 2003). In this context, the term "pharmabiotic" has been coined in order to describe the novel bioactive metabolites produced by the gut microbiota (Shanahan and Collins 2009). Addition of a specific probiotic bacteria or faecal matter from healthy individuals to polyphenol extracts in the dynamic Simulator of the Human Intestinal Microbial Ecosystem (SHIME) have shown to upregulate the bioavailability of the polyphenols by transformation into more accessible forms (Barroso et al. 2014, Jiménez-Girón et al. 2014). Konishi and Kobayashi (2004) experimentally proved that the major microbial metabolites of caffeic acid- m-coumaric acid, m-hydroxyphenylpropionic acid, and 3,4-dihydroxyphenylpropionic acid are transported across CACO-2 cells by the monocarboxylic acid transporter (MCT). It maybe rightfully concluded that bioavailability of the precursor polyphenols is very low and only after extensive metabolism by the gut microbiota they render better absorbability. So during evaluating the health benefits from specific food groups, the polyphenolic metabolites detected in plasma and/or urine should be considered to assign a beneficial role to them (Selma, Espín, and Tomás-Barberán 2009, Henning et al. 2013, Chiou et al. 2014, Xie et al. 2016). In the following portion we will be discussing about experiments that exemplify metabolism as the prime cogitation while ascertaining the bioefficacy of polyphenols. The contribution of the intestinal microbiota to the ameliorating activities of polyphenols exist in the gut and beyond.

4.1. Therapeutic activities of polyphenolic catabolites

The polyphenolic metabolites exhibited strong anti-inflammatory effects by suppressing secretion of targeted antibodies or any other inflammation inducing agents. Screening of microbial polyphenolic catabolites- hydrocaffeic, dihydroxyphenylacetic and hydroferulic acid revealed that they could reduce prostaglandin E_2 production by at least 50% in CCD-18 colon fibroblast cells previously stimulated with IL-1β. These compounds were also effective in alleviating inflammation among Dextran Sodium Sulfate induced mouse model of ulcerative colitis. Additionally hydrocaffeic acid was capable of reducing mucosal expression of cytokines TNF- α, IL-1β, IL-8, malonyldialdehyde levels, and oxidative DNA damage (Larrosa et al. 2009). Monagas et al. (2009) carried out a study on six healthy subjects to assess the effect of colonic metabolites of proanthocyanidins on the inflammatory response of lipopolysaccharide induced human peripheral blood mononuclear cells. The catabolites of proanthocyanidins particularly 3,4-dihydroxyphenylpropionic acid, 3-hydroxyphenylpropionic acid, and 3,4-dihydroxyphenylacetic acid have been shown to decrease the secretion of IL-1, IL-6, and TNF-α, thereby diminishing the inflammatory response to bacterial antigens, which otherwise could have possible ramifications such as chronic inflammatory or autoimmune diseases like Irritable Bowel Disease. Similarly upon injecting ferulaldehyde, a microbial metabolite of curcumin, intraperitoneally at a dose of 6 mg/kg, could depress the various markers of inflammation and prolong lifespan of LPS treated animals (Radnai et al. 2009). One study Hydroxyphenyl-γ-valerolactone suppressed NO production and iNOS expression more proficiently than its precursor catechin which was weakly active (Uhlenhut and Hogger 2012). Chen and Sang (2014) found that hydroxyphenyl-γ-valerolactone, the product of microbial fermentation of tea polyphenol was more competent than ascorbic acid and trolox in scavenging superoxide anions. In a very recent study, Taofiq et al. (2015) observed that the derivatives of p-coumaric acid had the strongest anti-inflammatory properties against LPS activated RAW 264.7 macrophages. In fact the methylated derivative displayed anti-inflammatory properties parallel to that of dexamethasone, which is used as standard. On the other hand the derivatives of p-hydroxybenzoic were inefficient to inhibit NO production. Piazzon et al. (2012) compared the antioxidative properties of ferulic and caffeic acid along with their sulphonated and glucuronated derivatives. Few derivatives like acyl glucuronide of ferulic acid, quercetin glucuronides and quercetin 3-O-sulfate retained their

antioxidant properties but rest of the compounds had exhibited extremely low antioxidation. The hydroxyl groups in the phenolic moiety imparts antioxidative properties to polyphenols. Considering the fact that both glucuronidation and sulfation occur at this site, antioxidative activities are immensely hampered in these metabolites. The authors thus conclude that conjugation reactions might boost or hinder biological activities depending upon the modification of chemical structure associated with it. Peron et al. (2017) treated urinary tract infections in rats by feeding cranberry juice and ascribed its antiadhesive activity against uropathogenic bacteria to the A-type procyanidin metabolites rather than their precursors.

Owing to their antioxidative and anti-inflammatory properties the polyphenolic metabolites provide protection and cure against metabolic disorders. Studies have validated the intense linear relationship between raised urinary levels of polyphenolic catabolites and weight loss (Calvani et al. 2010, Timmers et al. 2011, Aires et al. 2014, Hu et al. 2015). This has carved a pattern to develop aetiopathological knowledge on lifestyle diseases by identifying the blood and urinary markers inversely associated with prognosis of that disease (Reger et al. 2016, Rienks, Barbaresko, and Nöthlings 2017). Women's health study involving short term follow up of 1111 case control pairs with type 2 diabetes (T2D) after multivariate adjustment, associated higher urinary excretions of a flavanone derivative- hesperetin with a lower T2D risk (Sun et al. 2015). Numerous other studies have validated the inverse correlation between urinary concentrations of polyphenol metabolites and risk of metabolic disorders. Polyphenol catabolites generated by microbial activity have shown to prevent protein glycation which is synonymous with progression of the complications associated with diabetes. Particularly urolithin A and B, against ellagitannins, significantly reduced protein glycation at the physiological concentration of 1 mmol/L (Verzelloni et al. 2011). Tani et al. (2017) experimentally showed that delphinidin 3-rutinoside obtained from blackcurrant extract in intact form could increase glucagon like peptide (GLP-1) secretion from enteroendocrine L-cells in rats, subsequently improving glucose tolerance. Polyphenol metabolites experimentally have been found to curtail risk of ailments commonly associated with sedentary way of life like insulin resistance (Nøhr et al. 2016, Anhê et al. 2017), type 2 diabetes (Sun et al. 2014, Zhou et al. 2017), coronary heart diseases (Kilkkinen et al. 2006, Bresciani et al. 2014) and reduce mortality (Zamora-Ros et al. 2013).

The metabolite of flavonoids synthesised by intestinal microflora have cardioprotective effect. Takagaki and Nanjo (2015) in their study observed that epigallocatechin gallate (EGCG) metabolites could inhibit Angiotensin I-Converting Enzyme (ACE) in hypertensive rats. The flavonoid catabolite, 3-hydroxyphenyl propionic acid was found to be more potent than its precursor quercetin in mitigating blood pressure on both normotensive and spontaneously hypertensive rats by causing vasodilation (Najmanová et al. 2016). Recent studies provide substantial evidence in support of the atherosclerosis preventing attribute of ellagic acid derivatives (Mele et al. 2016). Likewise few studies did not find any significant difference in the baseline values between the treatment and placebo group (Alcorn et al. 2017).

4.2. Role of polyphenolic catabolites in prevention and cure of neurodegenerative diseases

Accumulating evidence indicates that gut microbiota possibly exerts influence on the overall brain functioning and behaviour of its host by communicating with the central nervous system through endocrine, neural and immune pathways (Cryan and Dinan 2012). This two way communication between the gut and brain (gut–brain axis) is well recognized with the gut microbiota viewed as a key regulator of this cross-talk. Pertinently the factors that precipitate the development of attention deficit hyperactivity disorder (ADHD) and/or associated manifestations are linked to dysbiosis of the microbial ensemble in gut, suggesting a link between gut microbiota and ADHD (Cenit et al. 2017). The interplay between polyphenols and gut microbiota is an effective tool for building resilience from cognitive impairment and mood disorders in susceptible subjects (Ward and Pasinetti 2016) and have been established by various studies. Verzelloni et al. (2011) studied the viability of oxidative stress induced human neuroblastoma SK-N-MC cells (following a 24 h exposure to 2 mmol/L DMNQ) in presence of polyphenol metabolites. The polyphenolic catabolites pyrogallol, urolithin B, dihydrocaffeic acid and 3-hydroxyphenylacetic acid at concentrations of 0.1, 0.5, 1, 5, 10 and 20 mmol/L, were effective in enhancing the viability of these neurones by 11–16% in comparison with the cells that haven't been exposed to polyphenol catabolites. On the basis of experimentation, moderate wine consumption is recommended to delay the onset of neurodegenerative diseases as the polyphenols derived from wine possess the ability to avert neuronal death induced by SIN-1 in a dopaminergic cell line (Pasinetti 2012, Esteban-Fernández et al. 2015). Wang et al. (2015) fed grape seed polyphenol extract to rats for a period of 10 days, the products of microbial metabolism like 3-hydroxybenzoic acid and 3-(3′-hydroxyphenyl) propionic acid were found to accumulate in their brain. Furthermore these particular metabolites play a key role in halting the progression of Alzheimer's disease pathogenesis by interfering with generation and assembly of β-amyloid peptides into neurotoxic β-amyloid aggregates. This finding is in good agreement to that of a previous study by Wang et al. (2010) that evaluates the effect of grape derived polyphenols on Alzheimer's disease. A latest study carried out on SAMP10 mice (a mouse model of brain senescence) by Pervin et al. (2017) revealed that epigallocatechin gallate had higher permeability and could reach the brain parenchyma. Epigallocatechin gallate was found to be more adept in improving learning ability, promoting human neuroblastoma SH-SY5Y cell growth and suppressing cognitive dysfunction than its microbial derivatives- epigallocatechin and gallic acid alone. However co-administration of epigallocatechin and gallic acid had more pronounced ameliorating effects comparable to that of epigallocatechin gallate, thus ensuring conservation of protective effects of their precursor even after hydrolysis

4.3. Cancer prevention with polyphenolic catabolites

Polyphenol metabolites have a credible role in cancer prevention and treatment. This fact is supported by the study

conducted by Prasain et al. (2016) who testified the inhibitory activities of cranberry derived metabolites on the growth of human bladder tumour cell lines by incubation with these compounds. Out of all the derived metabolites myricetin, quercetin, quercetin 3-O-glucoside, and isorhamnetin (3′-O-methylquercetin) displayed strong concentration-dependent anti-proliferative activities in bladder cancer cells with IC_{50} values ranging from 8–92 μM. Heleno et al. (2014) reported a higher cytotoxicity among the glucuronated and methylated derivatives of p-hydroxybenzoic, p-coumaric and cinnamic acid than the parent molecules when tested against five tumour cell lines. The authors claim that substitution of carboxylic group (in parent polyphenols) with an ester group and a hydroxyl group in the para position (in glucuronide derivatives of both p-coumaric acid and p-hydroxybenzoic acid) enhanced the cytotoxicity of the catabolites. Henning et al. (2013) even recommended that HCT-116 colon cancer cells could be treated in-vitro with metabolites obtained from tea polyphenols, 3,4-Dihydroxyphenylacetic acid and epigallocatechin gallate. The authors annotated that each of these metabolites even if present in little concentration, unanimously could exhibit an additive and pronounced antiproliferative effect. Forester and Waterhouse (2010) previously had endowed gallic acid, 3-O-methylgallic acid and 2,4,6-trihydroxybenzaldehyde as the most potent anti-carcinogenic agent among the anthocyanin metabolites. Recently Forester et al. (2014) demonstrated that these particular metabolites not only had a dose and time dependent inhibitory effect on Caco-2 cell viability but also on transcription factors like NF-κB, AP-1, STAT-1, and OCT-1 which are activated in colorectal cancer. De Molina et al. (2015) reported 12 fold higher anti-proliferative activity of 4,4′-di-O-methylellagic acid than its precursor ellagic acid against colon cancer cells and diminished chemo-resistance by down regulating Wnt signalling. Núñez-Sánchez et al. (2016) even suggested an effective proportion of the different ellagic acid derivatives for cancer prevention. More recently a study carried out by Yin et al. (2017) demonstrated that Urolithin C, one of the major catabolite derived from microbial degradation of Ellagic Acid and Ellagitanin was more cytotoxic and promoted apoptosis in PC12 cells compared to its precursor Ellagic Acid.

All the aforementioned studies demonstrated that the polyphenol metabolites had poor or no inhibitory effect on non-carcinogenic healthy cell lines even at high concentrations indicating that the cytotoxicity of polyphenol metabolites is inclusive to cancerous cells.

Umpteen studies on various cancer cell lines sanctioned the anti-proliferative and anti-carcinogenic effect of metabolites obtained from quercetin and chlorogenic acid/caffeic acid (Miene, Weise, and Glei 2011), resveratrol (Aires et al. 2013), catechin gallate (Chen and Sang 2014), ellagitannins (Cho et al. 2015, Wang et al. 2015, Sánchez-González, Izquierdo-Pulido, and Noé 2016). The mechanisms by which polyphenolic metabolites assist in cancer prevention include down regulation of Wnt signalling, COX-2 expression, up-regulation of GSTT2, p21 expression at mRNA and protein levels (Miene, Weise, and Glei 2011, Sánchez-González, Izquierdo-Pulido, and Noé 2016).

5. Synergistic action of probiotics and polyphenols

Probiotic bacteria metabolize polyphenols into bioactive compounds that results in epigenetic modulations pertaining to critical cell processes (Krautkramer, Rey, and Denu 2017). Supplementation of probiotics to a polyphenol-rich diet might enhance the potential ameliorating effects in comparison to polyphenol enrichment alone. Polyphenols can inhibit the activities of amylase and glucosidase and diminish the cariogenic potential of foods by reducing the tendency for such type of foods to serve as slow-release sources of fermentable carbohydrate (Zhang and Kashket 1998, McDougall et al. 2005, Da Costa et al. 2008). On the other hand probiotics can alter the metabolism by production of several potential health promoting metabolites like short chain fatty acids. It would be interesting to study the combined effect of polyphenols and probiotics in combination on obesity and associated multiple comorbidities like insulin resistance, dysglycemia, dyslipidemia, hypertension etc. The mechanisms exerted by polyphenol metabolites to prevent obesity has been outlined in Figure 3 (Baboota et al. 2013).

In a double-blinded randomized, crossover study, 6 men, and 10 women non-smokers with non-declared pathology were fed either 400 g of olive fruit polyphenol-enriched yogurt constituting 50 mg of encapsulated olive polyphenols (experimental group) or 400 g of plain yogurt (control group) every day for two weeks (Georgakouli et al. 2016). This lead to significant decline in body weight, body mass index (BMI), and hip-circumference values ($p < 0.05$) in the study group. However no significant effect on the complete blood count parameters in both the groups was observed except the LDL cholesterol level which seemed to decrease significantly ($p = 0.006$) in the experimental group. Another important effect that was observed owing to consumption of polyphenol-containing yogurt was significant decrease ($p < 0.05$) in thiobarbituric acid reactive substances (TBARS) levels. This is of considerable importance as the TBARS Assay determines lipid peroxidation.

In vitro studies using a combination of polyphenol and probiotics have been employed for detection of its ACE inhibiting properties. de Lacey et al. (2014a) demonstrated that incubation of probiotic bacteria *Bifidobacterium animalis* B94 with catechin and epigallocatechin solutions increased their ACE inhibiting properties after 24 hours which eventually declined after 72 hours. A special mention has to be made about the catechin solution, which has no inhibition against ACE when alone. Sarkar et al. (2015) in their study found that aqueous extracts of bartlett pear had moderate to low ACE inhibition whereas starkrimson pear extract had no inhibitory activity at all. This may be due to the higher antioxidant activity of the bartlett pear extract. Ahrén et al. (2015) fed 2 gm of a probiotic product consisting of blueberries fermented by *L. plantarum* to hypertension induced rats and observed a marked decrease in blood pressure levels from that of the control group within two weeks of supplementation. The fermented blueberry fraction

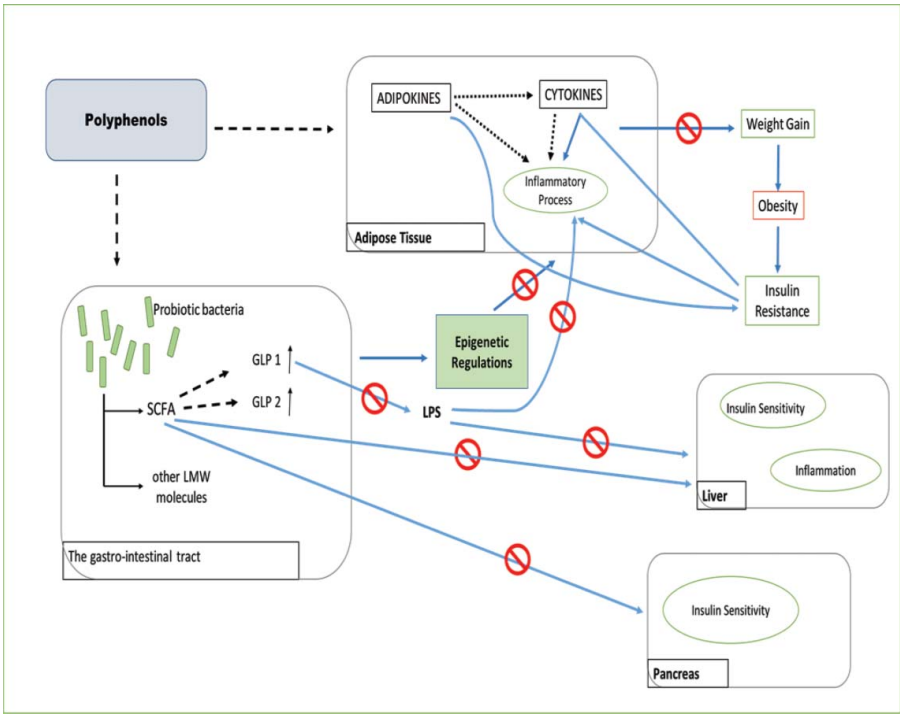


Figure 3. Graphical summary of some of the mechanisms involved in prevention of obesity exerted by polyphenol metabolites. Interactions of polyphenol with gut; gut microbiota; inflammatory molecules hormones/mediators; released by the adipose tissue. Dietary polyphenols may prevent adipogenesis through inhibition of preadipocyte to adipocyte differentiation, preventing lipid accumulation, modulation of adipokine secretion, down regulation of transcription factors, inhibition of lipogenic genes and/or through epigenetic regulation. Beneficial gut bacteria also helps in the secretion of gut hormones which suppress the activity of LPS and prevent its leakage into the circulation by enhancing intestinal barrier function and hence decreasing the obesity associated inflammation. (Baboota et al. 2013).

not only had a higher content of phenolic compounds but also certain phenolic acids that were otherwise absent in blueberry, had a more profound blood pressure lowering effect. The authors explained that the tannase producing *L. plantarum* strain may lead to an antihypertensive effect via an anti-inflammatory mechanism.

However in a double blind, randomised placebo controlled trial, when probiotics and fermented bilberries were consumed by hypertensive volunteers for 3 months no significant decline in blood pressure had been observed (Xu et al. 2015). The findings of Blanton et al. (2015) also do not support this hypothesis that probiotic supplementation augment antihypertensive effects of polyphenols instead they observed that supplemental probiotics diminishes the blood pressure lowering effect of blueberry consumption in spontaneously hypertensive rats. Rats consuming blueberry and blueberry plus probiotic showed a 75% and 45% reduction in systolic blood pressure rise from baseline to endpoint respectively compared to control rats. The supporting evidences from clinical trials with an objective of exploring amalgamating effect of polyphenols and probiotic consumption on human health is weak owing to substantial inter-individual variability. Tomás-Barberán, Selma, and Espín (2016) pointed out in their study that stratification of experimental group in accordance to their polyphenol-metabolizing ability would be a necessary and effective modification to yield more accurate and relevant results. Table 3 summarizes few clinical trials that had been conducted to evaluate the synergistic effects of probiotics and polyphenols in health promotion.

Different ailments have been found out to be characterized by gut dysbiosis, a condition associated with disparity in the relative proportion of Firmicutes to Bacteroidetes, where the ratio between the two increases (Mahowald, 2009, Jones et al. 2014, Carding et al. 2015, Robles-Vera et al. 2017). Rom et al. (2017) while exploring the effects of acrolein, an unsaturated aldehyde on atherosclerosis development found a major alteration at the phylum-level marked by increased Firmicutes and decreased Bacteroidetes among acrolein fed rats. Subsequently studies have furnished concrete evidence in defence of this hypothesis. Parkar, Trower, and Stevenson (2013) demonstrated that at concentrations 30 μg/mL, chlorogenic acid, caffeic acid, rutin and quercetin could reduce the firmicutes to bacteriodes ratio from 1.22 (in control) to 1.12, 1.10, 1.06 and 1.04 respectively. Anhê et al. (2015) fed cranberry extracts to HFHS (High Fat High Sucrose) induced obese mice and observed significant reduction in metabolism associated disorders by assisting in weight reduction, improved insulin sensitivity, lowering intestinal triglyceride content and treatment of intestinal inflammation and oxidative stress. These ameliorating effects of cranberry extract treatment was manifested by a marked increase in the proportion of *Akkermansia muciniphila*. In another study involving DIO (Diet Induced Obesity) mice model, Roopchand et al. (2015) corroborated this finding by demonstrating that grape fruit polyphenols not only raised the growth of *Akkermansia muciniphila* but also decreased the proportion of Firmicutes to Bacteroidetes, along with depression in symptoms of metabolic disorders. Polyphenol ingestion in native form (Qiao et al. 2014, Etxeberria et al. 2016, Most et al. 2017) or from various sources like cocoa (Tzounis et al. 2010) grapes (Choy et al. 2015, Roopchand et al. 2015), pomegranate juice (Mosele et al. 2015b, Rom et al. 2017), cinnamon bark and grape pomace (Van Hul et al. 2017) among in vitro models have claimed to

Table 3. Clinical trials assessing the synergistic ameliorating effects of polyphenols and probiotics on human health.

Objective of the study	Number & nature of the subjects involved	Species of Probiotics used	Polyphenols / polyphenolic rich food used	Outcome of the study	Reference
To assess the prebiotic potential of cocoa flavanols in a randomized, double-blind, crossover, controlled intervention study.	22 healthy adult volunteers were provided cocoa flavanol for 4 weeks.	*Bifidobacterium* and *Lactobacilli* species	Cocoa polyphenols	• The primary objective of the study was to see the increase in the counts of *Bifidobacterium* and *Lactobacilli* along with a decline in *Clostridia* counts. • This was synonymous with significant reductions in plasma triacylglycerol and C-reactive protein concentrations among the participants.	Tzounis et al. 2010.
To test the antihypertensive effect of bilberry containing live probiotic/ fermented bilberry in hypertensive adults in a double blind, randomised placebo controlled trial.	142 hypertensive adults with a stable dosage for antihypertensive medication over the last three months	*Lactobacillus plantarum*	Bilberries	• Consumption of the tested products for three months did not reduce the blood pressure in adults with hypertension. • The diversity and the composition of the oral and faecal microbiota remained significantly unaffected by the tested probiotic products.	Xu et al. 2015
To investigate the effects of an olive polyphenol-enriched yogurt on the haematological, physiological and metabolic parameters, blood redox status and body composition in a double-blinded randomized, crossover study.	16 participants (6 men, and 10 women) non-smokers with non-declared pathology	*Lactobacillus bulgaricus* and *Streptococcus thermophilus*	Olive fruit polyphenol-enriched yogurt	• This lead to significant decline in body weight, hip-circumference, body mass index (BMI) and blood pressure values in the study group. • No significant effect on the complete blood count parameters in both the groups was observed except for LDL cholesterol level which seemed to decrease remarkably. • Consumption of polyphenol-containing yogurt significantly reduced the levels of thiobarbituric acid reactive substances (TBARS).	Georgakouli et al. 2016
To evaluate the impact of consumption of yogurt along with lignans on cardiovascular disease in an elderly population by observations of the biomarkers of risk from a Cross-Sectional Approach in the PREDIMED Study.	7,169 Spanish elderly men and women at high cardiovascular risk who participated in the PREDIMED study.	*Streptococcus thermophilus*, and *Lactobacillus bulgaricus*	Lignan containing foods like wheat products, olive oil, red wine, asparagus, tomatoes, kiwis, and other fruits and vegetables and probiotic enriched yogurt.	• The consumption of both yogurt and lignans showed greater improvement in some cardiovascular health parameters than when consumed singly. • Subjects consuming both yogurt and lignans had significanty lower total cholesterol, triglyceride levels, LDL cholesterol, weight and body mass index.	Creus-Cuadros et al. 2017.

To explore the impact of symbiotic yogurt on blood pressure and lipid profile in a parallel, double-blinded, randomised trial	48 male and female volunteers, with mild to moderate hypercholesterolemia and hypertension, aged 30–65 years.	*Lactobacillus rhamnosus* and *Lactobacillus acidophilus*	Pomegranate juice concentrate	• The consumption of synbiotic yogurt resulted in 6% decrease in total cholesterol and 8.3% decrease in LDL cholesterol levels compared to controls. • Systolic blood pressure was reduced by 3.70 mmHg and diastolic blood pressure by 2.33 mm Hg. • No significant changes from the baseline were observed in triglycerides and HDL-C levels. • The atherogenic indices- Total cholesterol: HDLC ratio and LDL-C: HDL-C ratio decreased significantly in group that consumed synbiotic yogurt compared with the control group.	Miremadi, Sherkat, and Stojanovska 2017.
To compare the effect of probiotic supplementation with various polyphenol profiles, on the postprandial glucose and insulin responses in healthy young adults in a randomized, controlled, crossover study.	12 healthy young adults, 6 men and 6 women individuals (18–65 years) with no medication, no diagnosed allergy, and having BMI between 20 and 30 kg/m^2 with a stable body weight (<5% weight change in the last 3 months).	*Lactobacillus plantarum*	Five different beverages containing blackcurrant, bilberry, beetroot, mango and rose hip, enriched with probiotics	• Beverages containing blackcurrant, bilberry, rose hip or mango attenuated the early postprandial insulin response (0–90 min) significantly. • The drinks with bilberry or rose hip which reduced insulin response from the very early phase (0–30 min), • They did not show any effect on postprandial glycaemic response.	Xu et al. 2018.

result in an ecological shift in the microbiome causing a decline in the ratio of Firmicutes to Bacteroidetes. Firmicutes possess an unduly less number of glycan-degrading enzymes compared to Bacteroidetes (Mahowald et al. 2009). As a result of which the former are more repressed than the later by the antimicrobial properties of phenolic compounds. Inclusion of polyphenols in the diet facilitate the Bacteroidetes community to survive amicably. So it may be concluded that the selective growth promoting activity of polyphenols alters the ratio of resident bacterial species which yield desirable health effects. This might be a probable mechanism by which dietary polyphenols exert their weight lowering effect (Rastmanesh 2011).

This finding is compatible to the concept of total genetic count of gut as a prime determinant of health. According to which the people with impaired metabolic, inflammatory and hormonal status possess less microbial richness i.e.- they have a low gene count, compared to that of lean and healthy individuals who have a higher gene count (Cotilard et al. 2013, Le Chatelier et al. 2013). The decline in firmicutes to bacteriodetes ratio, the high gene count among healthy individuals and lastly the genetic constitution of the inhabitant bacterial species synonymously indicate the abundance of a particular species in health promotion.

6. Probiotic and polyphenols as food additives

Multiple studies have evinced that fermentation can enhance antioxidant activity in plant materials primarily due to rise in the concentration of phenolic compounds owing to microbial enzymatic reactions (Hur et al. 2014). Landete et al. (2014) attributes the aryl glycosidase activity of probiotic strains for increasing the antioxidant activity of glycosylated phenolic compounds. In view of this principle, polyphenol extracts of grape seed (Chouchouli et al. 2013), tea (Muniandy, Shori and Baba, 2014, Najgebauer-Lejko et al. 2014), olive pomace and grape marc (Aliakbarian et al. 2015) have been successfully incorporated in fermented milk and milk products to enhance antioxidant and antiradical activities over a prolonged period of time in order to provide additional value along with its known health benefits. de Lacey, López-Caballero, and Montero (2014) also demonstrated that incubation of green tea polyphenols with probiotic bacteria raised their antioxidant and antiradical properties. Xing et al. (2016) in their study, have successfully developed a novel bio-tofu by adding Fu brick tea extract into soymilk along with the probiotic *Lactobacillus plantarum* B1-6 and the increase in antioxidative activities were found to be in agreement to the aforesaid studies. Kwaw et al. (2017) designed an innovative study to investigate the optimum fermentation conditions to develop lactic acid bacteria fermented mulberry drink having the highest phenol, anthocyanin and flavonoid concentration and subsequent radical scavenging activity.

Enhancement in antioxidative and antiradical properties have opened up a new avenue for a natural method of preservation. The usage of naturally occurring compounds and biological entities singly or in various plausible combinations for preservation of physicochemical, sensory and microbiological quality of food materials is currently trending. Experimentations have been carried out using polyphenols along with probiotic bacteria to determine their effectivity for preservation purposes. Dry fermented pork loin prepared with the addition of *Lactobacillus rhamnosus* LOCK900 probiotic strain, 0.2% glucose, and 1.5% green tea extract had less oxidation reduction potential than controls after 21 days of ripening and 180 days of storage (Neffe-Skocińska et al. 2015). Lu et al. (2015) also demonstrated synergistic effects between the plant extracts (comprising tea polyphenols and essential oils of clove, cinnamon, anise, and ginger) and starter cultures (*Lactobacillus sakei* and *Staphylococcus xylosus*) against the growth of pathogenic bacteria and accumulation of biogenic amines in smoked horsemeat sausages.

7. Safety issues, limitations and health claims regarding probiotic and polyphenol usage

An unresolved challenge is to procure detailed information regarding the effective dose and intervals at which polyphenols must be consumed to yield beneficial effects. There is a bit of apprehension regarding the safety assessments for probiotics on both the immunologically compromised and immunologically naive host. New-borns, elderly, pregnant individuals and patients who are generally more susceptible to infectious disease might have elevated activation of the non-specific immune response following probiotic administration (Gill, Rutherfurd and Cross 2001). Studies have now confirmed that these effects pertaining to short term probiotic intervention are transient and recede gradually over a period of time. It must be mentioned here that there have been no reports claiming any harmful effects of probiotics in otherwise healthy but immunocompromised humans so far (Gueimonde, Ouwehand, and Salminen 2004, Sanders et al. 2010). Although there remains an urgent need for long term clinical studies dedicated to the assessment of safety and efficacy of probiotic supplementation especially among the immunocompromised population. Lack of complete knowledge regarding the mechanistic of probiotic action causes a major hindrance in predicting the safety of probiotic intervention.

On the other hand there are several reports of polyphenols inducing cytotoxicity and mutations or behaving as an anti-nutritional entity in food (Shoji et al. 2004, Mennen et al. 2005, Aron and Kennedy 2008). However these drawbacks are not alarming because of the relative low occurrence of polyphenols in food along with low bioavailability, which happens to be the main constraint in optimal functioning of polyphenols. The dosage at which polyphenols can cause adverse health impact is remarkably higher than what can be achieved pragmatically through dietary sources (Rusconi and Conti 2010). Furthermore no studies hitherto have come across any form of toxicity or pathogenicity in the combined usage of polyphenols and probiotics.

On the road to development of commercially viable functional food product, attestation of nutrition and health claims by the concerned governmental organization is a quintessential aspect. The European Food Safety Authority (EFSA, European Union), Food and Drug Administration (FDA, USA), Foods for Specific Health Use (FOSHU, Japan), takes utmost care while citing the health benefits in food labels to ensure maximal consumer protection (Miller 2015). They have a set of stringent rules and regulations which the manufacturers must comply with or else would

attract legal actions and penalty. The approval from these organisations comes only after substantial evidence is gathered in support of the particular claim. Most countries legally prohibit manufacturers from advertising any false, unsubstantiated, misleading, deceptive, claims that might create an erroneous perception with respect to the health benefit from that food (Miller 2015, Thomas 2016). Due to insufficient human clinical studies generating inadequate data on the beneficial effects of probiotics on human subjects, EFSA do not have a very positive feedback about health claims for probiotics (Rijkers et al. 2011, Katan 2012) whereas the FDA dictates that the investigation of probiotics in human trials must be filed as an 'Investigative New Drug' (Thomas 2016). Canada allows 17 probiotic species to make non-specific health claims, but disapproves any strain−specific health claims (Health Canada 2009). In order to bridge the discrepancy between scientific discovery and marketing hype more and more clinical research programmes need to be carried out, simultaneously the food industry must be encouraged to provide evidence backed detailed information regarding the composition, type, health effects of polyphenol-probiotic food products developed by them (Roberfroid 2000). This will holistically address all the issues regarding daily dietary recommendations, toxicity, safety and health claims.

8. Conclusion

All the ingested polyphenols must interact with the gut microbiota and reach the bloodstream, very few remain intact. Therefore the products of polyphenol biodegradation is of utmost importance while determining their biological property. The above studies corroborate that polyphenolic metabolites retain their biological properties in-vivo. In few instances, the native polyphenols might have presented more efficient antioxidant (Choudhury et al. 2015), anti-carcinogenic (González-Sarrías et al. 2014), anti-inflammatory properties but mostly it is the metabolites that get the opportunity to serve the purpose in biological systems.

Major investigations advocated inter individual variations in responses to generic medicine targeted for treatment of disease. Omics based personalised medicine is an emerging arena (Hamburg and Collins 2010) that is subject to facilitation by long term dietary intervention. So adequate polyphenol administration starting from early life will develop a desirable gut microbial population that would together form a tractable strategy for developing novel therapeutics assuring improved disease management. The studies are at a very nascent stage and further studies are needed to replicate these findings in order to explore potential mechanisms underlying the observed association. Enhanced precision in mimicking the complex gut environment in the form of simplified animal models or cell assays might ensure a better understanding about the mechanistic, effective dosage and toxic effects of probiotic-polyphenol functioning.

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