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Review

Polyphenols as *next-generation* prebiotics targeting intestinal mucosal tolerance

Carolina Ferreira [a,b,c,d], Pedro Vieira [a,b,c,d], Artur Figueirinha [e,f], Lígia Salgueiro [e,g], Maria Manuela Pintado [h], João Malva [a,b,c,d], Miguel Castelo Branco [d,i,j], Flávio Reis [a,b,c,d], Sofia Viana [a,b,c,d,e,*]

[a] Institute of Pharmacology & Experimental Therapeutics, Faculty of Medicine, University of Coimbra, Portugal
[b] Coimbra Institute for Clinical and Biomedical Research (iCBR), Faculty of Medicine, University of Coimbra, Coimbra, Portugal
[c] CIBB – Center for Innovative Biomedicine and Biotechnology, University of Coimbra, Coimbra, Portugal
[d] Clinical Academic Center of Coimbra (CACC), Coimbra, Portugal
[e] Faculty of Pharmacy, University of Coimbra, Coimbra, Portugal
[f] Associated Laboratory for Green Chemistry (LAQV) of the Network of Chemistry and Technology (REQUIMTE), University of Coimbra, Coimbra, Portugal
[g] Chemical Engineering and Renewable Resources for Sustainability (CERES), Department of Chemical Engineering, University of Coimbra, Coimbra, Portugal
[h] CBQF - Center for Biotechnology and Fine Chemistry, Associated Lab., School of Biotechnology, Catholic University, Porto, Portugal
[i] Coimbra Institute for Biomedical Imaging and Translational Research (CIBIT)-Institute for Nuclear Sciences Applied to Health (ICNAS), University of Coimbra, Coimbra, Portugal
[j] Institute of Physiology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal

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ABSTRACT

Polyphenols, long recognized for their antioxidant and anti-inflammatory properties, are widely consumed as dietary components or as constituents of functional foods and nutraceuticals. Emerging evidence, however, supports a paradigm shift beyond a purely redox-centered perspective, repositioning polyphenols as functionally relevant prebiotic phytochemicals with significant immunomodulatory capacity. This review frames polyphenols as *next-generation* prebiotics, emphasizing their capacity to act through coordinated, multi-layered mechanisms that extend beyond the stimulation of intestinal microbial growth. It examines how the gut ecosystem leverages their low systemic bioavailability and explores mechanisms linking their health benefits to microbiota-mediated intestinal mucosal tolerance as interconnected dimensions of prebiotic functionality. Emphasis is placed on the multimodal actions of polyphenol-derived microbial metabolites, increasingly recognized as *bona fide* postbiotics with therapeutic potential. These metabolites modulate key functional microbial outputs, including the secretion and cargo of bacterial extracellular vesicles, thereby regulating tolerogenic immune responses across the epithelial layer, lamina propria, Peyer's patches, and mesenteric lymph nodes. This integrated mode of action clearly distinguishes polyphenols from classical carbohydrate-based prebiotics, positioning them within a candidate functional category capable of targeting immune pathways in autoimmune and inflammatory diseases, including inflammatory bowel disease, diabetes and food allergies. The review further explores polyphenol-based prebiotic interventions driven by microbial functionality rather than taxonomic composition alone and highlights challenges and opportunities of polyphenols as tools in precision immunonutrition protocols where interventions are tailored to individual metabotypes, health status and metabolic variability.

1. Introduction

The use of natural products to modulate the gut microbiome and confer health benefits dates to the early 20th century, with the concept "prebiotic" first introduced in 1995 by Gibson and Roberfroid, who defined it as a "nondigestible food ingredient that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon, and thus attempt to improve host health" [1]. Although initially broad, it soon became clear that only a limited number of compounds, namely

* Corresponding author at: Institute of Pharmacology & Experimental Therapeutics, Faculty of Medicine, University of Coimbra, Portugal.
E-mail address: sofia.viana@ff.uc.pt (S. Viana).

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inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), fulfilled the proposed criteria. Moreover, important limitations became apparent, namely the unintended stimulation of non-probiotic bacterial species (including *Eubacterium biforme* and *Clostridium perfringens*) and inconsistency in both clinical outcomes and the expected modulation of gut microbiota (GM) composition and function [2]. Over time, the concept of prebiotics continued to evolve, prompting the need for a definition that encompassed non-carbohydrate substances, applications beyond the gastrointestinal tract, and categories other than food. As a result, in 2017 and more recently in 2024, the International Scientific Association for Probiotics and Prebiotics (ISAPP) issued updated definitions and scientific perspective inclusive of novel prebiotic candidates, namely polyphenols [3,4].

Polyphenols are structurally diverse bioactive compounds abundant in diverse medicinal plants and plant-based foods including colorful fruits and vegetables, red wine, chocolate and/or tea, which together provide an estimated average daily intake of 900–1000 mg [5]. Beyond their intrinsic antioxidant and immunomodulatory properties, polyphenols are catabolized into metabolites with enhanced bioactivity by a repertoire of enzymes expressed in intestinal polyphenol-metabolizing bacteria (e.g. *Bifidobacterium* and *Lactobacillus* species), inducing broad changes in the community structure of the gut microbiota (GM) [2,6–8]. Notably, they simultaneously support the reciprocal interactions between the GM and the immune system, wherein intestinal bacteria regulate multiple aspects of innate and adaptive immunity while being shaped by the immune system to maintain intestinal immune tolerance [9–11] Through this interplay, polyphenols emerge as key modulators of microbiota-driven immune regulation at the intestinal mucosa.

This review provides, for the first time, an integrative perspective of polyphenols as a candidate class of non-carbohydrate-based prebiotics that combine microbiota-dependent effects to direct host-targeted actions capable of modulating intestinal mucosal tolerance. Rather than acting through a single dominant mechanism, polyphenols likely exert a multi-layered set of effects at the intestinal mucosa that can contribute to reinforcing host–microbiota interactions, promoting immune tolerance, and generating effects beyond the gut. This integrated mode of action distinguishes polyphenols from classical carbohydrate-based prebiotics and supports their consideration as candidates within an expanded, functionally oriented prebiotic category with potential relevance for immune-mediated and inflammatory diseases.

2. Literature search and selection criteria

The PubMed and Scopus databases were searched (last accessed March 2026) using structured search queries combining “Prebiotics"[MeSH Terms], "Polyphenols"[MeSH Terms], "Phenols" [MeSH Terms], "Flavonoids"[MeSH Terms], "Tannins"[MeSH Terms], "Phenolic Acids", stilbene*, lignan*, "Gastrointestinal Microbiome" [MeSH Terms], "Immune Tolerance" [MeSH Terms], "Intestinal Mucosa/immunology" [MeSH Terms], “Postbiotics”, “Microbial phenolic metabolites”. Boolean operators (“AND”, “OR”) were applied as appropriate to refine and combine search terms. Inclusion criteria were: (i) original research articles or reviews reporting *in silico*, *in vitro*, or *in vivo* evidence of the prebiotic-like and immunomodulatory potential of polyphenols within the intestinal mucosa, with no restriction regarding year of publication; (ii) studies describing mechanistic pathways and molecular targets linking polyphenol microbial metabolism to intestinal immune tolerance; (iii) studies reporting clinical evidence on the effects of polyphenols on gut dysbiosis, immune responses, and/or the influence of metabotypes on interindividual variability in responsiveness; and (iv) peer-reviewed articles published in English. Exclusion criteria were: (i) conference and meeting abstracts; (ii) opinion pieces; (iii) commentaries; (iv) editorials; (v) working papers; and (vi) news articles.

3. Polyphenolic compounds: structural classes and natural footprints

Polyphenols are important dietary bioactive compounds derived from the secondary metabolism of plants and are responsible for several of their organoleptic properties, such as color, taste, bitterness and astringency. They play key roles in cell division, hormonal regulation, photosynthetic activity, germination, and reproduction, while also protecting plants from adverse abiotic and biotic stressors [12]. Accordingly, polyphenol profiles vary widely among plant species and tissues and are influenced by seasonal and geographical factors [13]. In plants, polyphenols originate from the aromatic amino acids L-phenylalanine or L-tyrosine, which undergo non-oxidative deamination to produce the phenylpropanoids cinnamic and p-coumaric acids. These molecules serve as direct precursors of stilbenoids and flavonoids through complex biosynthetic pathways initiated by their conversion into the corresponding coenzyme A thioesters. Once synthesized, polyphenols can be further modified by glycosylation, methylation, acetylation, or other acylation reactions, generating a wide array of chemical structures typically associated with increased water solubility and stability [13].

This large and heterogeneous family of over 10,000 phytochemicals constitutes one of the most numerous and widely distributed groups of natural products. They range from simple phenolic molecules to complex polymers and are characterized by an aromatic ring containing one or more hydroxyl groups in their chemical structure [14]. The number and characteristics of phenolic structural units not only allow the classification of polyphenols into distinct subgroups with defined chemical structures, such as phenolic acids, flavonoids, tannins, lignans, and stilbenes [15,16], but also largely determine their bioavailability, microbial biotransformation, and subsequent biological activity. Structural features including degree of polymerization, glycosylation, and hydroxylation patterns influence their intestinal absorption and the extent to which they reach the colon available for gut microbial metabolism. In general, highly polymerized compounds, including tannins and proanthocyanidins, exhibit lower intestinal absorption and undergo extensive catabolism by the gut microbiota, generating low-molecular-weight phenolic metabolites with enhanced bioavailability and biological activity. Likewise, glycosylation and hydroxylation patterns modulate substrate accessibility to microbial enzymes and shape the spectrum of metabolites produced, ultimately influencing host responses. These microbial-derived metabolites are increasingly recognized as key mediators of polyphenol-induced effects, including the modulation of intestinal barrier integrity, inflammatory signaling pathways, and mucosal immune tolerance. Therefore, the chemical structure of polyphenols is not only central to their classification but also determines their functional interactions with the gut microbiota and their subsequent immunoregulatory properties. The following sections summarize the main chemical characteristics, dietary sources, and structural particularities of the principal polyphenol subclasses, as illustrated in Fig. 1.

3.1. Phenolic acids

Phenolic acids, characterized by a single carboxylic acid group, fall into two main categories based on their carbon skeletons: hydroxybenzoic acids (C6–C1) and hydroxycinnamic acids (C6–C3) [15,17]. Frequently found hydroxybenzoic acids include p-hydroxybenzoic, protocatechuic, ellagic, gallic, vanillic, and syringic acids. On the other hand, chlorogenic, caffeic and ferulic acids are the most prevalent hydroxycinnamic acid found in the diet. Sources of phenolic acids are fruits, vegetables, seeds, legumes, cereals, and coffee, in which they are mostly found in bound forms like esters, amides, or glycosides [18]. For instance, hydroxybenzoic, coumaric, ferulic, gallic, vanillic, and syringic acids are found in different types of grains and cereal, including wheat, oats, rice, corn, and triticale, among others [19]. Phenolic acids are also found in fruits such as mango, apples and citrus fruits, coffee, red wine

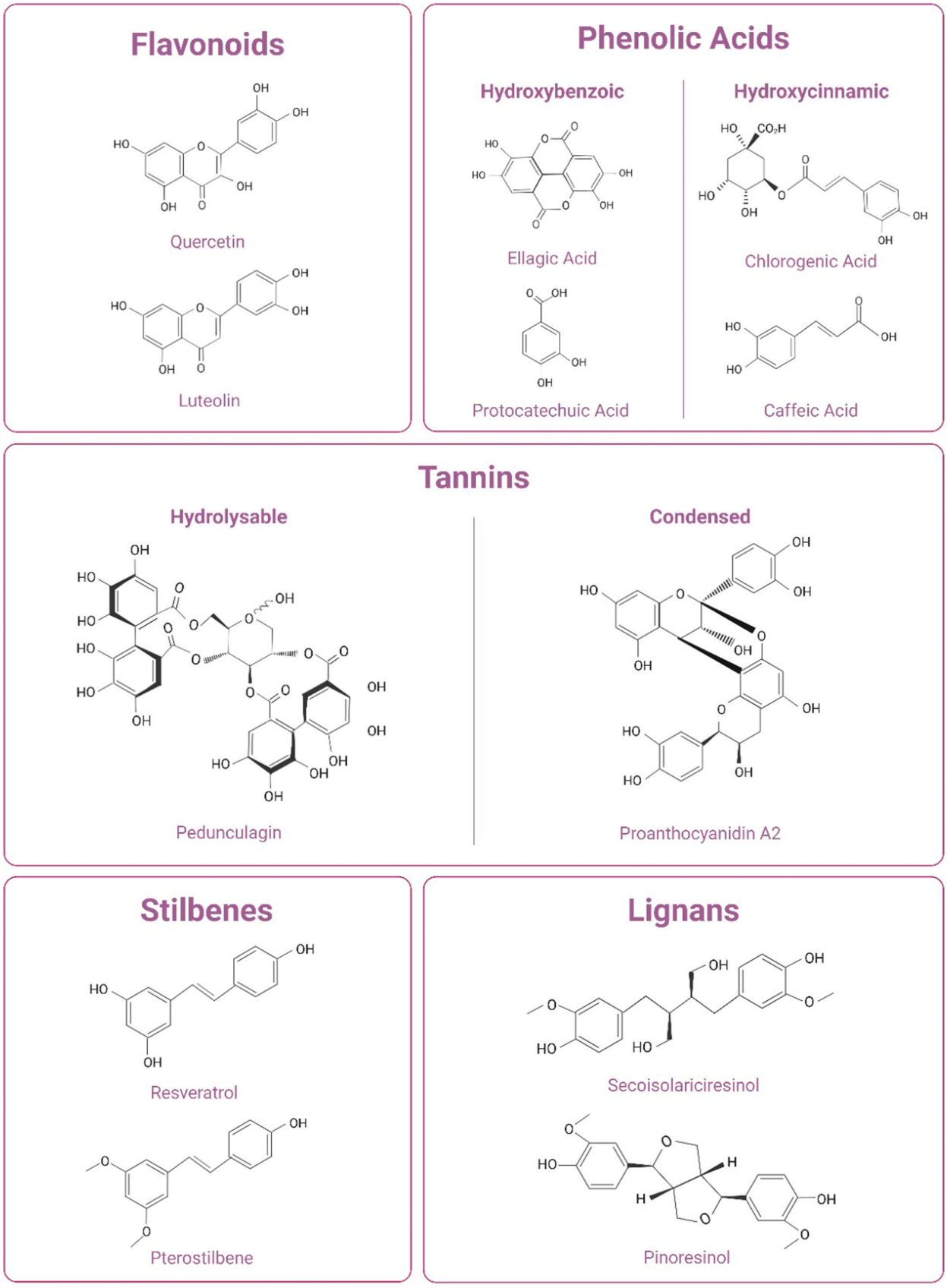

Fig. 1. Representative examples of the major polyphenol classes: flavonoids, phenolic acids (hydroxybenzoic and hydroxycinnamic acids), tannins (hydrolysable and condensed), lignans, and stilbenes. Figure created in BioRender.com.

and nuts [17].

3.2. Flavonoids

Flavonoids share a common C6–C3–C6 backbone consisting of two aromatic rings linked by a three-carbon unit, which in most subclasses cyclizes to form an oxygenated heterocycle. Variations in the hydroxylation pattern, oxidation state and/or saturation of this central pyran ring define the major flavonoid subclasses, including flavones, flavonols, flavanones, flavanols, isoflavones, and anthocyanidins, as depicted in Fig. 2 [20]. Flavonoids can be found in most vegetables (e.g., onions, kale, spinach), fruits (e.g., apples, grapes, berries), herbs and spices (e.g., parsley, capsicum pepper) as well as cocoa, coffee and black and green tea [15,21].

3.3. Stilbenes

Stilbenes present a C6-C2-C6 backbone, consisting of two phenyl rings linked by a methylene bridge. Based on their structural complexity, they are categorized as either simple stilbenes or poly-stilbenes. In plants, stilbenes are typically produced as a defense response to stress or injury, which limits their presence in the human diet. Nonetheless, stilbenes have attracted increasing interest due to their potential health benefits. Among them, resveratrol is the most extensively studied, commonly found in grapes- and by extension, red wine - as well as in berries and peanuts, for example [15,17].

3.4. Lignans

Lignans are a diverse class of compounds formed through the polymerization of two phenylpropanoid units, resulting in considerable structural variability. They are widely distributed in fiber-rich plant sources, including legumes, mainly soybeans and chickpeas, vegetables such as carrots and broccoli, and cereals like barley and oats [15]. Among dietary sources, linseed stands out as the richest, particularly in secoisolariciresinol, a prominent phytoestrogen [22].

3.5. Tannins

Tannins are broadly classified into two main types - condensed and hydrolysable - based on their ability to be broken down by acids [15,23]. Condensed tannins, also known as proanthocyanidins, are made up of polymers and oligomers of polyhydroxy flavan-3-ol and flavan-4-ol units, which are classified as A-type or B-type according to their interflavan linkages; B-type proanthocyanidins are more prevalent in the human diet, whereas A-type proanthocyanidins, although less frequent, are often associated with greater biological activity [24]. In contrast, hydrolysable tannins - further classified in gallotannins (e.g. tannic acid) or ellagitannins (e.g. punicalagin) - are polyester compounds formed by the esterification of hydroxybenzoic acids and their derivatives with glucose or other polyols [15,23]. Hydrolysable tannins can be hydrolyzed by acids, bases and specific enzymes. Tannins are present in a wide range of dietary sources - including vegetables, legumes, seeds, nuts,

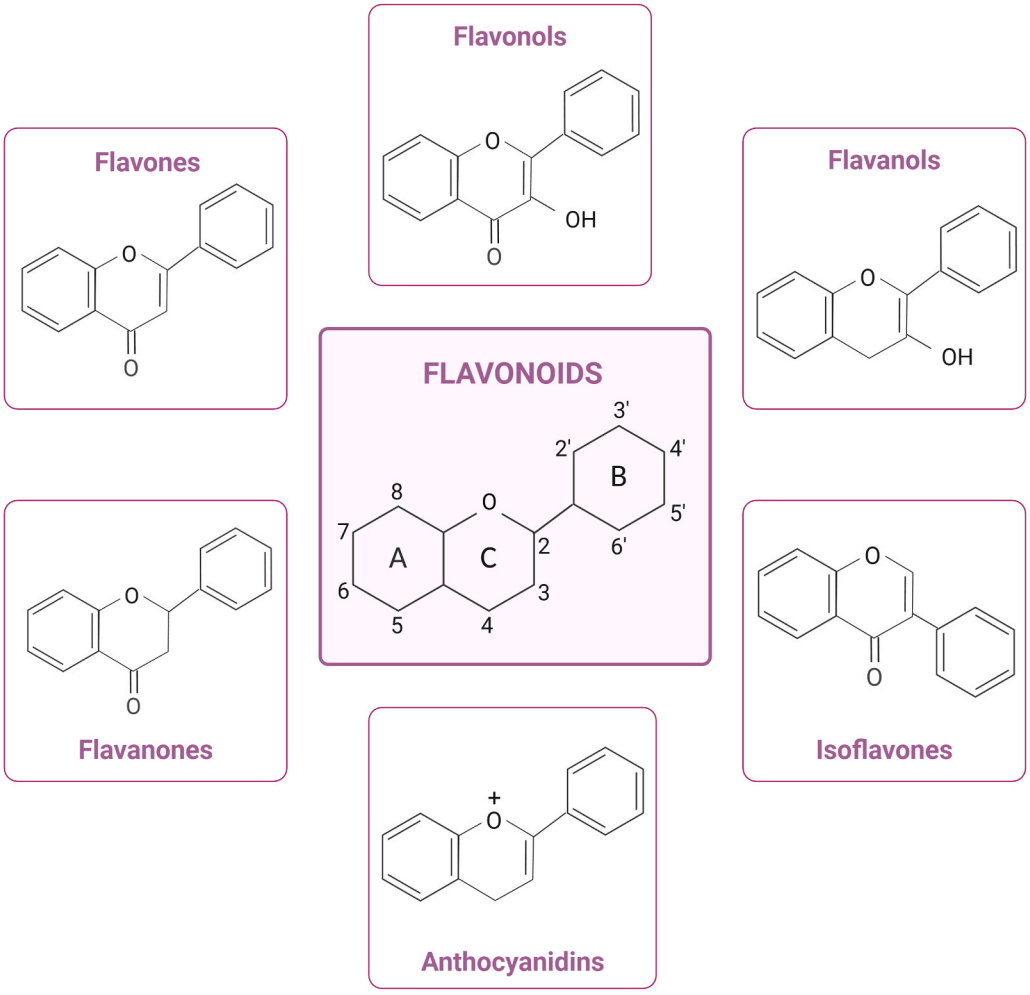

Fig. 2. General chemical structure of flavonoids, showing the A, B, and C rings and carbon numbering, and representative structures of the major flavonoid subclasses. Figure created in BioRender.com.

cereals, cacao, tea, and coffee - and significantly influence the sensory characteristics of these foods and beverages, especially their astringency, bitterness, aroma, and mouthfeel [23].

4. From ingestion to action: gut microbiota as key regulators of polyphenols metabolism and bioactivity

4.1. Polyphenols absorption and metabolism

Despite their wide range of purported health benefits, polyphenols exhibit generally low bioavailability in humans. Only an estimated 5–10% of ingested polyphenols are absorbed in the small intestine, where they undergo substantial biotransformation reactions within enterocytes [25,26]. The remaining 90–95%, predominantly oligomeric and polymeric forms, pass to the colon largely intact, where they are subjected to extensive microbial metabolism by the gut microbiota, yielding smaller, structurally simpler metabolites that are more readily absorbed and often retain or even enhance bioactive potential [25–27].

Generally, polyphenols are not present in plants as free molecules but are instead bound to sugars mainly through α- and β-glycosidic linkages either to a hydroxyl group (O-glycosides) or directly to a carbon atom of the aromatic ring (C-glycosides). Accordingly, polyphenols deglycosylation is a key first step for their absorption and further hepatic metabolism. Host metabolism of polyphenols is largely limited to specific deglycosylation reactions and hepatic phase II conjugations with glucuronic acid, sulfate or glutathione. These conjugations render the metabolites more hydrophilic and facilitate their urinary excretion or their enterohepatic recirculation to the intestine, where they may undergo further transformation by the GM [28].

Whereas O-deglycosylation can be mediated by mammalian enzymes such as lactase-phlorizin hydrolase expressed in the intestinal epithelium, C-glycosides are resistant to enzymatic cleavage by the host. Accordingly, polyphenols undergo microbial transformations comprising deglycosylation, decarboxylation, dehydrogenation, demethylation, and α- and β-oxidation, among other reactions [26,29–31]. The resulting metabolites are then distributed via the bloodstream to various target organs before being ultimately excreted in the urine. In contrast to the parent polyphenolic compounds which are typically detected in circulation only at nanomolar concentrations, phenolic metabolites can reach substantially higher systemic levels. This is attributed to their reduced molecular size and altered polarity following microbial and host metabolism, which can favor intestinal absorption and systemic persistence. These metabolites are therefore considered key players of polyphenol-associated biological effects [32]. While some controversy remains regarding the extent to which deglycosylation is required for polyphenols absorption, there is strong evidence that their biological effects are strongly influenced by their metabolic transformation by the intestinal microbiota [22], a process that depends fundamentally on the phenolic structure, polymerization degree and spatial configuration [16,30].

4.2. Polyphenols microbial metabolism

The health effects of many polyphenols often depend less on the native compounds themselves and more on the transformations they undergo in the gut. To date, no mammalian enzymes have been identified that can cleave the core three-ring structure characteristic of flavonoids [33]. Instead, the genome of several beneficial colonic microbes encodes an array of (poly)phenol-associated enzymes (PAZymes) involved specifically in polyphenol biotransformation into smaller metabolites with enhanced bioavailability. PAZymes-producing species include members from Coribacteriaceae, Eggerthellaceae, and Lactobacillae, which have the capacity to release phenolic metabolites that may benefit commensal microbiota and host health [34,35]. Functionally characterized microbial enzymes span several catalytic classes, including hydrolases (e.g., lactase/phlorizin hydrolase, phloretin hydrolase), reductases (e.g., enoate reductase, daidzein reductase, tetrahydrodaidzein reductase), dioxygenases (e.g. quercetinase), isomerases (e.g., chalcone isomerase), racemases (e.g. dihydrodaidzein racemase), and decarboxylases (such as phenolic acid decarboxylase), among others. Fig. 3 provides a structural overview of the microbial catabolic pathways associated with representative flavonoids (e.g. quercetin, daidzein) and other polyphenolic compounds (e.g. pedunculagin), illustrating the sequential biochemical reactions leading to their respective bioactive metabolites.

In the case of flavonoids, gut bacteria can cleave the C-ring at several positions, yielding a wide variety of simple phenolic derivatives originating from the A- and B-rings. The hydroxylation pattern and structural arrangement of the B-ring strongly influence the resulting metabolic products. After C-ring fission, further microbial reactions, such as demethylation and dehydroxylation, generate phenolic acids or aldehydes substituted with one to three hydroxyl or methyl ester groups [28]. A representative example is the fate of flavones, such as luteolin and apigenin, which are converted into phenylpropionic and phenylacetic acid derivatives, including 3-(3-hydroxyphenyl)propionic and 3,4-dihydroxyphenylacetic acids. These transformations are driven primarily by flavonoid-degrading anaerobic consortia dominated by *Eubacterium ramulus* and related taxa, alongside secondary transformation by reductive Actinobacteria such as *Eggerthella lenta*.

Both compounds exert significant health-promoting effects, particularly related to mitigating metabolic syndrome, where they decrease blood pressure [36], modulate lipid metabolism, and oxidative stress pathways [37]. Likewise, flavanones such as naringenin and hesperidin are converted into the monophenolic acids phloroglucinol and phenylpropionic acid derivatives. Initial deglycosylation and structural modifications are facilitated by gut microbes such as *Flavonifractor plautii*, while carbohydrate-acessing bacteria such as *Bacteroides thetaiotaomicron* enhance substrate availability through glycosidic bond degradation [38].

Flavonols such as quercetin and kaempferol undergo C-ring cleavage and oxidative transformations, yielding protocatechuic acid (PCA) and 2,4,6-trihydroxybenzoic acid, among other intermediates [39]. Quercetin degradation is catalyzed by microbial dioxygenases, including quercetinase activity reported in *Bacillus subtilis,* which uses molecular oxygen to cleave the heterocyclic C-ring [40]. The resulting metabolites have shown to exert broad anti-inflammatory and immunomodulatory effects by suppressing pro-inflammatory cytokine production (e.g., TNF-α, IL-6, IL-1β) [41], inhibiting key inflammatory mediators and enzymes such as nitric oxide (NO), prostaglandin E2 (PGE2), inducible nitric oxide synthase (iNOS), and cyclooxygenase 2 (COX-2) [42], improving gut barrier function by enhancing tight junction (TJ) proteins expression [43], and downregulating central signaling pathways such as nuclear factor kappa B (NF-κB), MAPK, and NLRP3 inflammasome activation [44].

Anthocyanins are rapidly deglycosylated by lactic acid bacteria, particularly Bifidobacterium spp. and Lactobacillus spp. initially hydrolyzing them into simple sugars and phenolics, which are subsequently metabolized into bioactive phenolic acids and aldehydes such as 3-hydroxycinnamic acid, 3,4-dihydroxybenzoic acid, and 4-hydroxybenzoic acid [29,45]. Isoflavones follow similar microbial transformations. The soybean-derived compound daidzein is involved in a series of reduction steps mediated by specialized Eggerthellaceae and Coriobacteriaceae members, such as *Adlercreutzia equolifaciens* and *Slackia isoflavoniconvertens*, to produce the phytoestrogens (S)-equol and O-desmethylangolensin (O-DMA) [46]. Equol has shown to be physiologically relevant, exerting anti-inflammatory, antioxidant, antitumor, and estrogen-like effects [47]. It has shown to mitigate lipopolysaccharide (LPS)-induced inflammatory responses in both murine microglia cells [48,49] and macrophages [50]. Additionally, equol is able to suppress the expression of IL-6 and its receptor *in* vivo [51], leading to reduced C-reactive protein (CRP) and tumor necrosis alpha (TNF-α) levels [52]. Furthermore, a study evaluating the effects of

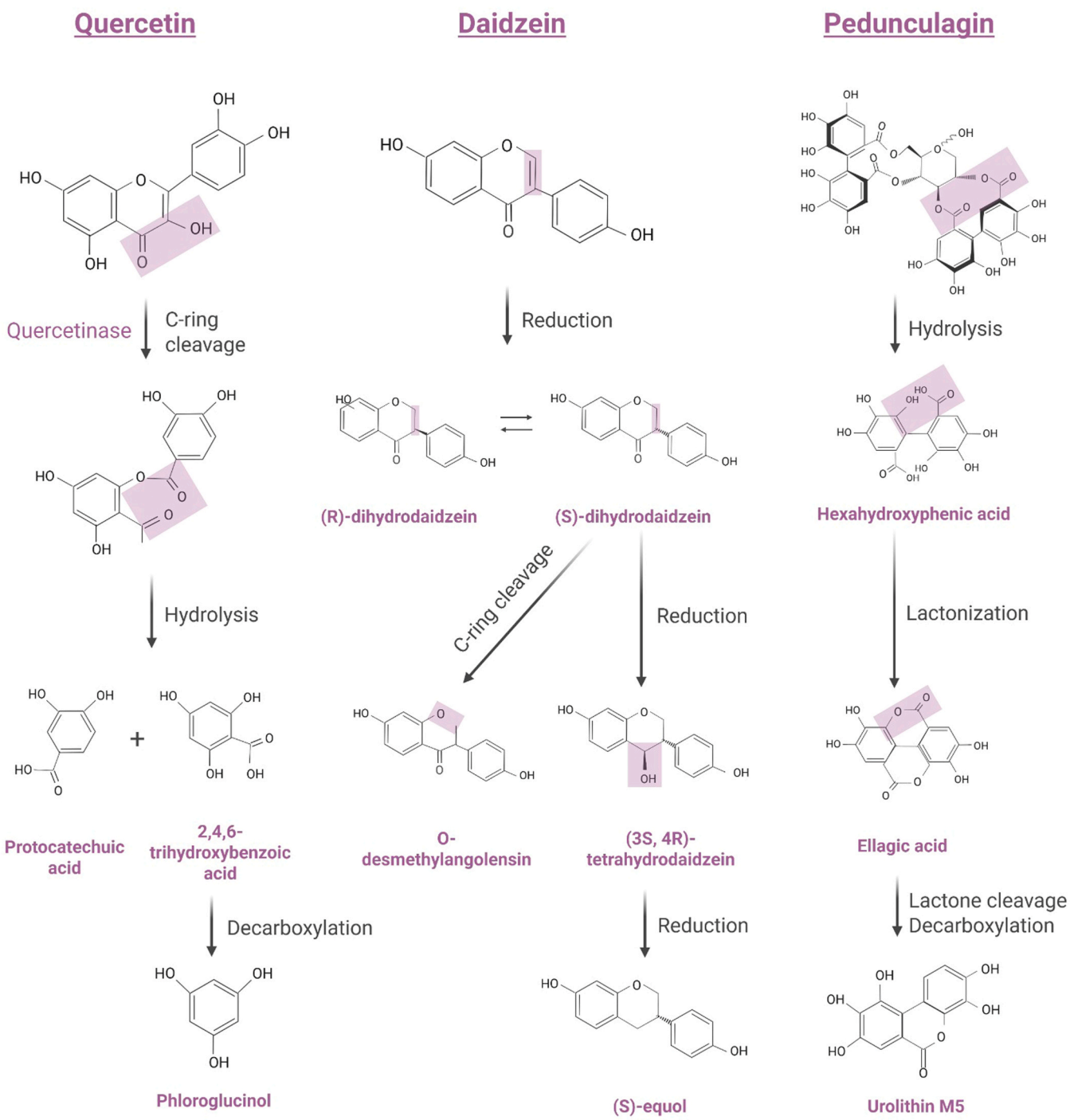

Fig. 3. Microbial catabolic pathways of representative polyphenols (quercetin, daidzein and pedunculagin). Figure created in BioRender.com.

indole-3-acetic acid administration in mice with DSS-induced colitis reported enhanced the production of equol from *Bifidobacterium pseudolongum,* which resulted in an increased ratio of forkhead box P3 $(Foxp3)^{+}$ T cells in colon tissue and alleviated disease severity [53].

Other polyphenolic compounds, including condensed and hydrolysable tannins, lignans, stilbenes, as well as phenolic acids, exhibit greater structural and polymeric heterogeneity than flavonoids. As a result, their absorption in the small intestine varies according to their chemical complexity, which in turn determines the extent to which they reach the colon and become available to microbial metabolism. Oligomeric and polymeric structures of flavan-3-ols, called proanthocyanidins or condensed tannins (e.g., proanthocyanidin A2) are precursors of a range of low-molecular-weight phenolic acids, including benzoic, phenylacetic, and phenylpropionic acid derivatives. These transformations are mediated by fermentative species, namely *Lactobacillus plantarum*, yielding bioactive compounds such as 3-hydroxyphenylpyruvic acid. This metabolite has shown to inhibit foam-cell formation *in vitro* [54], suggesting a potential role in modulating early atherogenic processes.

Hydrolysable tannins undergo microbial hydrolysis by tannin acylhydrolase–producing bacteria, generating gallic acid (from gallotannins) and ellagic acid (from ellagitannins). These intermediates are further metabolized into urolithins through dihydroxylation, decarboxylation and lactonization reactions

by microorganisms such as *Gordonibacter* spp. and *Butyrivibrio* spp [55,56]. In particular, urolithin A (UroA) consistently demonstrates broad anti-inflammatory and immunomodulatory activity. Beyond decreasing pro-inflammatory cytokine production in multiple cell types, including bone marrow macrophages [57] and colonic epithelial cells [57,58], UroA also enhances host defense mechanisms by modulating antitumor immune responses [59–61] and strengthening the intestinal barrier [57,58,62]. The latter is considered to result from two different mechanisms: 1) upregulation of TJ proteins, including zonula occludens-1 (ZO-1), occludin and claudin-4 [57,58], and 2) colonic

Table 1
Identification of polyphenol-metabolizing bacteria, their principal metabolic pathways and the resulting phenolic metabolites derived from microbial transformation of representative polyphenol classes.

Class Subclass	Substrate(s)	Functional group Representative taxa	Reaction	Metabolite(s)	Reference
FLAVONOIDS					
Flavones	Apigenin Luteolin	**Primary polyphenol degraders:** *Eubacterium ramulus* *Blautia glucerasea* **Secondary phenolic transformers:** *Eggerthela lenta*	C-ring cleavage	3-(3-hydroxyphenyl)-propionic acid 3-(4-hydroxyphenyl)-propionic acid	[28,30]
Flavanones	Hesperidin Naringenin	**Primary polyphenol degraders:** *Flavonifractor plautii* **Matrix-degrading generalists:** *Bacteroides thetaiotaomicron*		3-(3-hydroxyphenyl)-propionic acid Phloroglucinol	[28,30]
Flavonols	Quercetin	**Primary polyphenol degraders:** *Flavonifractor plautii* **Dioxygenase-producing bacteria:** *Bacillus subtilis*		2,4,6-trihydroxybenzoic acid Protocatechuic acid	[28,30]
	Kaempferol 3-O-glucoside	**Glycoside-hydrolyzing bacteria:** *Bifidobacterium spp.*	Deglycosylation Hydrolysis	Kaempferol (aglycone)	[30,66]
Flavanols	Epigallocatechin Gallocatechin	**Isoflavone-metabolizing Eggerthellaceae:** *Adlercreutzia equolifaciens* *Slackia equolifaciens*	Dihydroxylation	3-(3-Hydroxyphenyl)propionic acid 3-(3,4-Dihydroxyphenyl)propionic acid 5-(3′,4′-Dihydroxyphenyl)—valerolactone	[30,66]
	Epicatechin Catechin	**Secondary phenolic transformers:** *Eggerthela lenta*	C-ring cleavage	5-(3′,5′-Dihydroxyphenyl)–valerolactone	
Isoflavones	Daidzein	**Isoflavone-metabolizing Eggerthellaceae:** *Adlercreutzia equolifaciens* *Slackia equolifaciens* *Slackia isoflavoniconvertens*	Reduction Dihydroxylation	Equol	[30,66]
		Glycoside-hydrolyzing bacteria: *Bifidobacterium spp.*	Hydrolysis		
		Secondary fermenters: Clostridium spp.	C-ring cleavage	O-Desmethylangolensin	
Anthocyanins	Cyanidin Malvidin	**Glycoside-hydrolyzing bacteria:** *Bifidobacterium spp.* *Lactobacillus spp.*	Deglycosylation	3-hydroxycinnamic acid 3,4-Dimethoxybenzoic acid 3,4-Dihydroxybenzoic acid 4-Hydroxybenzoic acid	[30,66]
PHENOLIC ACIDS					
Hydroxybenzoic acids	Gallic acid	**Anaerobic fermenters:** *Bacteroides spp.* *Bifidobacterium spp.* *Clostridium spp.* *Eubacterium spp.*	Decarboxylation Dihydroxylation C-ring cleavage	Phenylacetic acid Benzoic acid	[28,30]
Hydroxycinnamic acids	Chlorogenic acid	**Glycoside-hydrolyzing bacteria:** *Bifidobacterium spp.* *Lactobacillus spp.*	Reduction Decarboxylation	3-(3-hydroxyphenyl)-propionic acid 3-(3,4-dihydroxyphenyl)-propionic acid 3-(4-hydroxyphenyl)-propionic acid	
STILBENES					
	Resveratrol	**Isoflavone-metabolizing Eggerthellaceae:** *Adlercreutzia equolifaciens* *Slackia equolifaciens*	Reduction Decarboxylation	3,4′-dihydroxy-trans-stilbene Lunularin 4-hydroxydibenzyl	[66,68]
LIGNANS					
	Secoisolariciresinol	**Anaerobic fermenters:** *Bacteroides spp.* *Bifidobacterium spp.* *Clostridium spp.* *Eubacterium spp.*	Demethylation Deglycosylation Reduction Dihydroxylation	Enterodiol Enterolactone	[30,66]
TANNINS					
Condensed	Proanthocyanidins	**Primary depolymerizers:** *Gordonibacter urolithinfaciens* *Bifidobacterium pseudocatenulatum* *Butyrivibrio spp.* **Secondary fermenters:** *Clostridium spp.* *Eubacterium spp.*	C-ring cleavage β-oxidation	3-phenylpropionic acid 4-hydroxyphenyl acetic acid 3-(4-hydroxyphenyl) propionic acid p-coumaric acid Pyrogallol Pyrocatechol	[69]
Hydrolysable	Ellagitannins	**Ellagitannin-to-urolithin converters:** *Gordonibacter urolithinfaciens* *Bifidobacterium pseudocatenulatum*	C-ring cleavage Decarboxylation Dihydroxylation	Urolithins	[69]

mucus thickening [62], both via modulation of aryl hydrocarbon receptor (AhR)- and nuclear factor erythroid 2-related factor 2 (Nrf2)-dependent signaling [57,62]. Clinical trials have further confirmed UroA's immunomodulatory properties, showing that it induces relevant transcriptional shifts in pathways linked to inflammation and metabolism across immune populations [63].

Lignans are also substrates for complex microbial transformation involving deglycosylation, reduction, demethylation, dihydroxylation, and lactonization. Through a multistep metabolic sequence that encompasses diverse precursor molecules, intermediate metabolites, conjugation patterns, and bacterial species, lignans are ultimately converted into the enterolignans enterodiol and enterolactone [64], which have shown to exert anti-inflammatory activity [65]. These transformations are mediated by functionally diverse anaerobic communities, including members of *Bacteroides*, *Bifidobacterium*, *Clostridium*, and *Eubacterium* [66]. Phenolic acids such as gallic and chlorogenic acids, although structurally simpler than other polyphenolic classes, undergo microbial ester hydrolysis, giving rise to hydroxyphenylpropionic acids and related derivatives. For example, chlorogenic acid supplementation leads to the appearance of hippuric, benzoic, and cinnamic acids in plasma and urine, confirming their microbial origin [67]. Table 1 summarizes the principal metabolic pathways and biotransformation products associated with the major classes of polyphenols in humans.

4.3. The core role of metabotypes

Research on polyphenols has consistently highlighted substantial interindividual differences in their bioavailability and physiological effects. In this context, individual variations in GM composition and functionality have emerged as a key factor in explaining, at least in part, the observed differences in the biosynthesis of microbiota-derived polyphenol metabolites [70–72]. Accordingly, individuals can be stratified into distinct polyphenol-related metabotypes that reflect differences in microbial metabolic capacity. These metabotypes are characterized by specific sets of metabolites arising from the microbial catabolism of defined polyphenol precursors within a given microbial ecosystem [71]. They are primarily determined on the basis of qualitative criteria, namely the ability or inability to produce certain metabolites (producers *versus* non-producers) and are therefore only marginally affected by external factors such as diet, gastrointestinal transit time, food matrix effects, or the timing of sample collection. To date, clearly characterized polyphenol-related metabotypes are mainly associated with the metabolic pathways of isoflavones and ellagic acid [64,73].

Isoflavones undergo extensive biotransformation by the GM, generating a wide range of metabolites that depend on both the individual microbial composition and the chemical structure of the parent isoflavone. These metabolites include dihydrodaidzein, dihydrogenistein, tetrahydrodaidzein, tetrahydrogenistein, O-desmethylangolensin (O-DMA), (S)-equol, and 5-hydroxy-(S)-equol, among others [39]. The conversion of daidzein into equol represents the most thoroughly characterized polyphenol-related metabotype, although growing interest has also focused on O-desmethylangolensin (ODMA) metabotypes. Key transformations in daidzein catabolism involve modifications of the 4H-pyran-4-one C ring, which may be cleaved to form O-DMA and related metabolites (the most common route), or undergo sequential saturation and specific dehydroxylation reactions, yielding (3S)-equol, the only enantiomer produced by the human GM [74]. Bacteria capable of equol production harbor an extensive enzymatic repertoire, including daidzein reductase (DZNR), daidzein racemase (DZRC), dihydrodaidzein reductase (DHDR), and tetrahydrodaidzein reductase (THDR) [75]. A number of equol-producing bacterial species have been identified in the human gut, including *S. equolifaciens*, *S. isoflavoniconvertens*, *A. equolifaciens*, *Eggerthella* sp. YY7918, and *Lactobacillus paracasei* CS2 (JS1), among others [76].

Likewise, the low bioavailability of tannins results in their extensive biotransformation in the distal colon region by the intestinal microbiota. Microbial metabolism encompasses lactone-ring cleavage, decarboxylation, and dehydroxylation reactions, ultimately leading to *6 H*-dibenzo [*b,d*]pyran-6-one derivatives, collectively known as urolithins [64]. Three urolithin metabotypes have been identified: urolithin metabotype A (UMA), defined by the production of urolithin A derivatives; urolithin metabotype B (UMB), which in addition to these also produce urolithin B and isourolithin A; and urolithin metabotype zero (UM0), representing non-producers [77]. Bacterial species including *Lactobacillus plantarum*, *Lactobacillus paraplantarum*, and *Lactobacillus pentosus* exhibit tannin acyl hydrolase activity, potentially explaining the consistent prebiotic effects of polyphenols and their capacity to enhance the growth of intestinal lactobacilli [78]. Notably, over 30% of the genera differentiating UM-A and UM-B are classified within the Eggerthellaceae family [77].

The metabolism of flavanones, proanthocyanidins, anthocyanins, lignans, prenylflavonoids and stilbenes also exhibits pronounced inter-individual variability, characterized by gradients in metabolite production that distinguish "high producers" from "low producers" of specific metabolites. Nevertheless, no distinct human metabotypes have been identified for their metabolism [73,79].

Clinical evidence indicates that microbial metabotypes are associated with distinct clinical outcomes. In human cohorts, equol-producers consistently exhibit more favorable cardiometabolic profiles, including attenuated dyslipidemia [80] and reduced risk of metabolic syndrome [81], when compared with non-producers. Analogously, stratification based on urolithin metabotypes revealed differences in fatty acid metabolism and tryptophan catabolism between UM-A and UM-B individuals, modulating intestinal barrier integrity as reflected by circulating ZO-1 levels [82]. Additionally, combined metabotype profiling integrating equol, urolithin and lunularin production further reinforces the importance of microbial metabolic capacity in shaping clinical outcomes. Intervention studies on pre- and post-menopausal women showed that higher polyphenol-metabolizing capacity was associated with improved physiological responses after polyphenol supplementation, reducing vasomotor symptoms and enhancing life quality of post-menopausal women [83]. Ongoing clinical research is expected to further reinforce this framework. The PolyPause trial (NCT07182370) is currently evaluating the distribution of polyphenol metabotypes in menopausal women consuming polyphenol-enriched capsules (e.g., resveratrol, ellagic acid and daidzein) for 8 weeks. By integrating circulating and urinary phenolic-derived metabolite profiling with untargeted urinaru metabolomics, this study intends to characterize interindividual variability in metabolic responses to polyphenol supplementation and identify metabolite signatures associated with cardiovascular risk modulation [84].

Collectively, these findings highlights that the biological effects of polyphenols are closely determined by their chemical structure, which governs their intestinal absorption, microbial accessibility, and metabolic fate. Through the coordinated action of gut microbial enzymes, structurally diverse polyphenols are transformed into a broad range of bioactive metabolites with distinct immunomodulatory and barrier-protective properties. Importantly, interindividual differences in gut microbial composition and metabolic functionality further influence the generation of these metabolites, giving rise to distinct metabotypes associated with variable host responses and clinical outcomes. These observations reinforce the concept that the health effects of polyphenols depend not only on their intrinsic chemical properties, but also on their dynamic interactions with the gut microbiota, supporting their emerging recognition as a functionally relevant class of microbiota-modulating compounds with prebiotic-like properties.

5. Beyond antioxidants: *Next-gen* polyphenols-derived prebiotics

5.1. Polyphenols' duplibiotic activity

Polyphenols represent a more sophisticated means of modulating the gut ecosystem than conventional prebiotics. Notably, their limited bioavailability can be advantageous in this context: it ensures that substantial amounts reach the colon, where they become substrates for microbial biotransformation while simultaneously exerting selective growth-promoting or inhibitory effects on specific microbial taxa [2]. More recent research has been highlighting them as *duplibiotics*, an emerging concept describing unabsorbed substrates that modulate the GM by both antimicrobial as well as growth-stimulating effects. Accordingly, polyphenols comprise a hybrid strategy that offers a more nuanced way to shape the gut ecosystem compared to traditional prebiotics or antimicrobials alone, favoring a eubiotic intestinal state.

Polyphenols exert antimicrobial activity through multiple complementary mechanisms targeting microbial survival and colonization capacity [85]. One of the most consistently reported effects is the inhibition of biofilm formation, which compromises bacterial persistence and pathogenicity. For example, resveratrol (0–25 μg/mL, 24 h) reduced *Fusobacterium nucleatum* biofilm formation *in vitro* [86], while EGCG and penta-O-galloyl-β-D-glucose (100 μM, 48 h) inhibited biofilms in *Pseudomonas* spp. [87]. In parallel, several polyphenols interfere with microbial nutrient acquisition and intracellular functions. Tannic acid suppresses the growth of *Enterobacter cloacae*, *Escherichia coli*, and *Clostridium clostridioforme* through iron chelation [88], whereas flavonoids such as quercetin and kaempferol (35 μM, 2 h) impair bacterial DNA replication by inhibiting DNA gyrase B and PriA helicase activities, respectively [89,90]. Another important mechanism involves the attenuation of bacterial communication and membrane integrity. Polyphenols can interfere with quorum sensing (QS) pathways, thereby reducing virulence-associated signaling, as demonstrated by an orange extract rich in O-glycosylated flavanones (200 μg/mL, 24 h) against *Yersinia enterocolitica* [91,92]. Additionally, membrane destabilization appears to be a recurrent antibacterial effect, particularly against Gram-negative bacteria [26]. This mechanism has been reported for luteolin–quercetin–ceftazidime combinations [93], EGCG against *Streptococcus pyogenes* (10 μM, 30 μM, or 50 μM) [94], tea polyphenol mixtures (375 μg /mL) in *Serratia marcescens* [95], and berry extracts in *Salmonella* and *E. coli* cultures [96].

Collectively, these findings suggest that polyphenols do not act through a single antimicrobial pathway but rather through a multifactorial and potentially synergistic mode of action involving biofilm inhibition, nutrient deprivation, interference with bacterial replication and membrane disruption. This multimodal activity may contribute to their ability to selectively suppress pathogenic microorganisms while preserving or even favoring beneficial microbial populations. Notably, polyphenols stimulate the growth of intestinal bacteria with key biological roles. Evidence from pure culture studies has shown that numerous strains belonging to the genera *Lacticaseibacillus, Lactiplantibacillus*, *Lactobacillus, Bacteroides* spp. can be stimulated by polyphenols likely due to their ability to utilize these compounds as trophic substrates [97,98]. *In vivo* studies in invertebrates, vertebrates as well as human studies confirm the rise in beneficial gut bacteria, namely *Lactobacillus* and *Bifidobacterium spp*., following polyphenol supplementation [26]. A meta-analysis performed by Ma *et al.* described a 220% and 56% increase in *Lactobacillus* and *Bifidobacterium* abundances, respectively, in result to supplementation with polyphenols [99]. Mango pulp and peel have particularly shown promising prebiotic effects, leading to elevated *Lactobacillus* and *Bifidobacterium* counts *in vitro* [100], as well as an interesting preventive profile regarding the loss of beneficial bacteria associated with high-fat diets (HFD) in mice [101]. In humans, the same has been observed for several polyphenols and polyphenol-enriched compounds, including anthocyanins and flavonoids [102], berries [103,104], cocoa-derived flavanol drink [105], green tea [106] and red wine [107], among others. Some of these effects seem to have a significant impact on healthy individuals' metabolism, since cocoa flavanols-induced expansion of *Bifidobacterium* and *Lactobacillus* seemed to correlate with decreased plasma triglycerides and CRP levels [105], and red wine polyphenols have also shown to reduce blood triglycerides and CRP concentrations, as well as lower blood pressure and decrease total and high-density lipoprotein (HDL) cholesterol as a result of GM modulation [108].

Taken together, the available evidence supports the concept that polyphenols act as multifunctional modulators of the gut ecosystem rather than as conventional antimicrobial or prebiotic agents alone. Importantly, these microbiota-related effects appear to extend beyond intestinal homeostasis, potentially contributing to improvements in multi-organ dysfunctions.

5.2. Polyphenols-derived postbiotics

According to Tsilingiri *et al.*, postbiotics encompass a broad range of substances that are released by or generated through the metabolic activity of microorganisms and that exert direct or indirect beneficial effects on the host [109]. These compounds confer health benefits via mechanisms similar to those attributed to probiotics, while potentially reducing the risks associated with the administration of live microorganisms. Consequently, much like prebiotics, postbiotics are considered to have a favorable safety profile, while potentially retaining efficacy comparable to that of probiotics [110]. Notably, microbial metabolism of polyphenols yields diverse metabolites that are increasingly recognized as new frontiers postbiotics with promising therapeutic value [27], warranting further investigation to properly distinguish the effects of those generated in situ by the gut microbiota following polyphenol intake from those resulting from the exogenous administration of the same compounds.

5.2.1. Polyphenols-derived microbial metabolites

In contrast to large polyphenolic polymers, microbial-derived metabolites exhibit higher bioavailability than their polyphenolic precursors and can readily cross cell membranes, including the blood–brain barrier. As a result, they exert pharmacological effects by acting as stimulatory, inhibitory or signaling molecules [111]. Phenolic metabolites have pronounced effects on host well-being, contributing to the regulation of GM composition, the reduction of oxidative stress, the reinforcement of intestinal barrier function, the inhibition of inflammatory responses, and the modulation of immune responses [112]. Well-known phenolic postbiotics include urolithin A, a metabolite derived from ellagitannins degradation, associated with reduced cardiometabolic risk. Its safety following oral administration has been demonstrated in human clinical trials, together with improvement in fatty acid oxidation rate and systemic mitochondrial health [113]. Similarly, *(S)*-equol derived from the isoflavone daidzein, has shown therapeutic potential in the management of estrogen-related cancers [114], menopausal syndrome and cardiovascular diseases [115]. Notably, a one-year trial of 10 mg/day equol supplementation in middle-aged Japanese women reported a significant reduction in arterial stiffness [116], while a parallel, long-term intervention using the same dose in postmenopausal women demonstrated a marked increase in whole-body bone mineral density [117]. Overall, these data support the concept that microbial phenolic metabolites act as key bioactives intermediates through which polyphenols-derived prebiotics exert systemic health benefits.

5.2.2. Short-chain fatty acids

An alternative mechanism through which polyphenols exert prebiotic effects involves the modulation of microbial short-chain fatty acids (SCFAs) production resulting from the fermentation of plant-derived polysaccharides. The main SCFAs, acetic, propionic, and butyric acids,

are considered key regulators of both innate and adaptive immune responses to microbial colonization. They act by modulating fundamental immune mechanisms, including cell proliferation and apoptosis, phagocytosis, activation of the NLRP3 inflammasome, and chemokine signaling pathways, among others [118,119].

Notably, both *in vitro* and *in vivo* studies have consistently highlighted the capacity of polyphenols to stimulate saccharolytic microbial metabolism, thereby enhancing SCFAs biosynthesis. For example, chlorogenic acid, rutin, caffeic acid and quercetin at 100 μg/mL have been shown to promote bacterial butyrate and propionate production in human GM culture models [120]. These observations have been further corroborated by *in vivo* experiments, in which supplementation with hesperidin [121] or blackcurrant [122] resulted in increased SCFAs levels in the cecum of Wistar and Sprague-Dawley rats. Importantly, the influence of polyphenols on gut microbial metabolism is closely linked to therapeutic outcomes. In this regard, polyphenol administration via green tea [123] or mango-based beverages [124] was found to increase the abundance of SCFA-producing bacteria, particularly *Akkermansia*, thereby alleviating experimental colitis.

Polyphenols not only influence microbial SCFAs biosynthesis but also modulate the fecal excretion of bile acids (BAs). Several bacterial taxa, including members of the Firmicutes, Bacteroidetes, and Actinobacteria phyla, express bile salt hydrolase (BSH) enzymes that catalyze BAs deconjugation, rendering them more hydrophobic, less efficiently reabsorbed, and therefore more readily excreted into feces [125]. Following deconjugation, primary BAs are further transformed by Firmicutes, particularly genera such as *Clostridium* and *Eubacterium*, into secondary BAs via 7-dehydroxylation [126,127]. Beneficial reductions of total and low-density lipoprotein (LDL) cholesterol have been reported in humans consuming tea flavan-3-ol monomers, such as catechins, an effect associated with enhanced fecal excretion of secondary BAs [128]. These metabolic changes were accompanied by an increased abundance of members of *Clostridium coccoides*, particularly *E. rectale*, which are known both for their role in secondary BAs formation and for their probiotic function in butyrate synthesis from dietary carbohydrates. Similarly, a study showed that healthy men consuming 272 mL of red wine per day for 29 days experienced a reduction in total cholesterol levels, an effect linked to alterations in *Bifidobacterium* abundance with BSH activity [108]. Nevertheless, further research is needed to determine whether these effects are driven primarily by the parent polyphenols or by their microbial-derived metabolites.

5.2.3. Bacterial extracellular vesicles

Polyphenols can modulate both the secretion and cargo of bacterial extracellular vesicles (BEVs), adding a new layer to their microbiota-mediated effects. BEVs are emerging as central mediators of microbiota-host immune interactions, contributing to goblet cell function and the maintenance of the luminal mucus barrier [129–131]. These non-replicative nanostructures are released by both Gram-negative and Gram-positive bacteria, functioning as inter- and intraspecific communication vehicles that allow horizontal transfer of BEV cargo to the cytoplasm of the recipient cell [132]. Owing to their distinct physical, biochemical, and biofunctional properties, BEVs have attracted growing interest for the development of novel therapeutics, vaccines, and delivery systems [133]. Notably, BEVs can readily cross the intestinal barrier and reach distal organs and have even been suggested as a novel mechanism underlying GM-brain crosstalk within the gut–brain axis. Polyphenols have been shown to modulate signaling pathways involved in extracellular vesicle biogenesis, thereby enhancing EV secretion [134,135]. Moreover, polyphenols can alter BEV cargo (e.g. nucleic acids, miRNA, proteins, phenolic metabolites) and surface composition, enabling BEVs to act as protective nano-delivery systems that shield polyphenols from degradation, ultimately improving their stability, circulation time, and therapeutic efficacy [136]. Resveratrol, for example, has been shown to induce the release of extracellular vesicles enriched with gut-derived microbial metabolites, such as dihydroresveratrol and lunularin, in healthy rats [137]. Similarly, a study performed in Sprague-Dawley rats treated with 50 mg/kg of chlorogenic acid for 1 week showed an enrichment of *Bacteroides acidifaciens*-derived BEVs with anti-inflammatory properties, which enhanced mucosal barrier integrity and alleviated experimental irritable bowel syndrome [138].

Together, these findings support the notion that BEVs may act as mediators of polyphenol-induced responses across greater distances and over prolonged periods of time [139].

5.3. Polyphenols and gut microbiota-mucosal immunity crosstalk

The gastrointestinal mucosa is a highly complex system composed of a semi-permeable barrier that limits the passage of luminal microorganisms, antigens and toxins while allowing the translocation of nutrients, water, and selected microbial metabolites from the intestinal lumen into the circulation [140,141].This dynamic structure comprises the GM, a monolayer of epithelial cells mechanically interconnected by TJs, and the gut-associated lymphoid tissue (GALT), encompassing the luminal mucus layer, multifollicular Peyer's patches and numerous isolated lymphoid follicles distributed along the intestine, as well as the appendix in humans [140–142].

The GM and the immune system engage in a reciprocal and tightly regulated relationship, whereby intestinal bacteria regulate several aspects of the immune response while being shaped by the immune system to maintain homeostasis and immune tolerance [9–11]. In recent years, research investigating the benefits of polyphenol supplementation on gut mucosal integrity and overall health has expanded substantially. Polyphenols are xenobiotics and act as mild physiological stressors capable of eliciting protective effects through preconditioning mechanisms that activate endogenous defense pathways, akin to hormesis or trained immunity [143,144]. In this context, polyphenols exhibit robust immunomodulatory properties by fine-tuning immune cell metabolism through a multimodal mechanism that includes the regulation of nutrient-sensing pathways, the balance of AMPK/mTOR signaling, inter-organelle communication, and epigenetic reprogramming [7].

Within the intestinal milieu, polyphenols exert immunomodulatory effects through multiple and interconnected axes that are strongly influenced by the GM. Their so-called *duplibiotic* activity, encompassing both selective growth-promoting or inhibitory effects on specific microbial taxa and the extensive microbial metabolization into bioactive postbiotics (e.g. phenolic metabolites, SCFAs, BEVs), act synergistically to reinforce mucosal barrier function while amplifying polyphenols immunomodulatory effects at extra-intestinal compartments. Fig. 4 provides an overview of the prebiotic actions of polyphenols and their immunomodulatory effects across distinct intestinal mucosal compartments, including the epithelial barrier, lamina propria, Peyer's patches, and mesenteric lymph nodes.

5.3.1. Polyphenol-mediated modulation of intestinal epithelial barrier integrity

Evidence from animal models suggests that polyphenol-induced immunomodulation may be initiated at the level of the epithelial barrier. Notably, supplementation with polyphenols has been associated with an expansion of goblet cell populations, leading to increased luminal secretion of mucin-2 (MUC2) and enhanced TJ density, thereby strengthening epithelial cohesion and barrier integrity [145]. Such effects have been reported following supplementation with polyphenols derived from grape seeds (*Vitis vinifera* L. cv. Chardonnay) [146], cranberry fruit (*Vaccinium macrocarpon* spp.) [147], loquat fruit (*Eriobotrya japonica*) [148], and *Lycium ruthenicum*, a traditional Chinese medicinal plant [149].

5.3.2. Polyphenols immunomodulatory actions within the lamina propria

Beneath the intestinal epithelium, within the loose connective tissue layer known as the lamina propria (LP), polyphenols modulate both non-

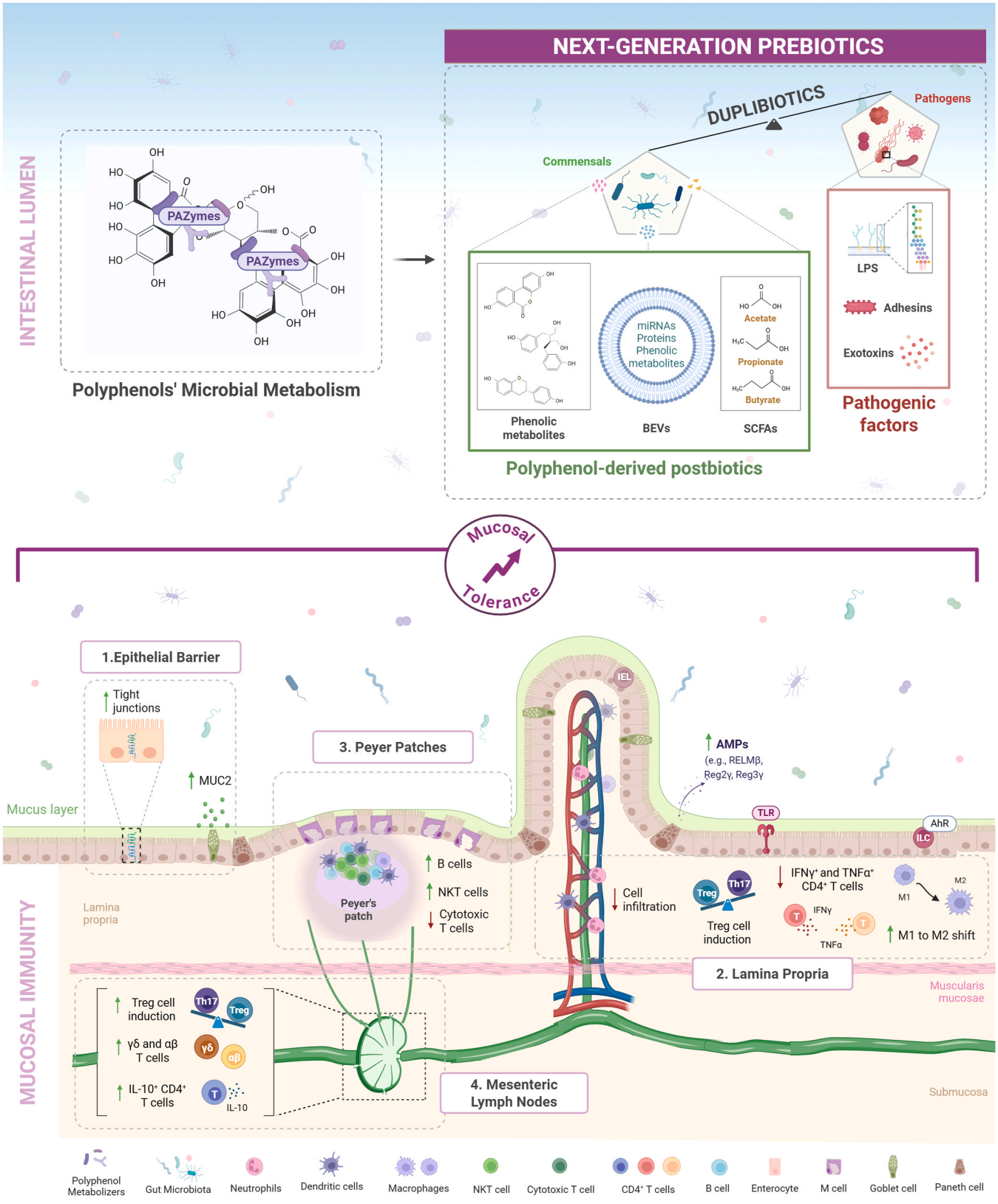

Fig. 4. Integrated overview of the prebiotic actions of polyphenols in shaping intestinal mucosal immunity. Polyphenols exert selective antimicrobial pressure against pathobionts while promoting the growth of beneficial microbial taxa, a phenomenon referred to as the *dupliotic effect*. Simultaneously, they stimulate the generation of polyphenol-derived postbiotics, including polyphenol microbial metabolites, bacterial extracellular vesicles, and short-chain fatty acids. These coordinated and multilayered processes at the intestinal mucosa reinforce symbiotic host-microbiota interactions and promote immune tolerance across distinct mucosal compartments, encompassing the epithelial barrier, lamina propria, Peyer's patches, and mesenteric lymph nodes. Figure created in BioRender.com.

cellular defense mechanisms and innate and adaptive immune responses that collectively contribute to protection against pathogen invasion. Supplementation with polyphenols obtained from grape seeds (*Vitis vinifera* L. cv. Chardonnay) [150], Mueloliva extra virgin olive oil (*Olea europaea*) [151], and Zhenjiang aromatic vinegar [152] has been shown to reinforce the LP by upregulating antimicrobial peptides (AMPs), including RELMβ (resistin-like molecule beta), Reg2γ, and Reg3γ (regenerating family member gamma). These AMPs contribute to the establishment of a hostile microenvironment that neutralizes invading microorganisms, restricting pathogen entry [146,151,152].

In parallel, isolated polyphenols such as kaempferol, curcumin, and chlorogenic acid attenuate the intestinal infiltration of innate immune cells, including neutrophils and DCs, from the bloodstream into the LP [153–155]. Quercetin further promotes macrophage polarization toward an anti-inflammatory M2 phenotype, while reducing the frequencies of interferon gamma (IFN-γ)$^+$ and tumor necrosis alpha (TNF-α)$^+$ CD4$^+$ T cells in the colonic LP of mice with colitis [156]. Modulation of adaptive immunity was also evident in colitic mice fed a diet supplemented with 4.5% lyophilized Aronia berry powder (*Aronia melanocarpa*, cv. Viking), which decreased T helper (Th)17 cell abundance while favoring the expansion of regulatory T (Treg) cells within the LP [157].

5.3.3. Polyphenols regulation of lymphocyte responses in Peyer's patches

At the level of organized lymphoid structures, polyphenols further regulate immune surveillance of luminal antigens by modulating specific lymphocyte subsets within Peyer's patches. Cocoa polyphenol-enriched extracts obtained from natural cocoa powder (*Theobroma cacao* L., var. Forastero) have been shown to reduce the proportions of T helper and cytotoxic T cells while increasing the frequencies of natural killer T (NKT) cells and B cells [158]. However, conflicting results have been reported regarding the effects of polyphenols on secretory immunoglobulin A (IgA) production [149,158–160]. Further studies by Massot-Cladera and colleagues suggest that cocoa-induced microbial and immunological alterations in Peyer's patches may be linked to changes in Toll-like receptor (TLR) expression profiles, highlighting a potential mechanism underlying polyphenol-mediated immune sensing [161].

5.3.4. Polyphenol-driven immune cell remodeling in mesenteric lymph nodes

The immunomodulatory effects of polyphenols extend beyond the intestinal mucosa to the mesenteric lymph nodes (MLNs), a key site for antigen presentation and immune cell priming. Supplementation with cocoa polyphenols (*Theobroma cacao* L., var. Forastero) [160] or hesperidin [159] has been shown to increase the proportions of γδ and αβ T-cell subsets within MLNs. Likewise, curcumin [162] and resveratrol [163] supplementation promotes the expansion of CD4$^+$ interleukin 10 (IL-10)$^+$ and Foxp3$^+$ Treg cells while concomitantly reducing Th17 cell frequencies in MLNs, reinforcing an anti-inflammatory immune milieu.

6. Polyphenol-derived prebiotics as promising nutraceuticals to enhance intestinal mucosal tolerance

The composition, diversity and functional capacity of the GM profoundly influence the architecture of the mucosa and mucosa-associated immune responses, playing a central role in maintaining intestinal homeostasis [11,164,165]. The intestinal microbiota constitutes a fundamental element of the immunological environment that supports the establishment of oral tolerance. Host sensing of microbial signals within the gut directs GALT-mediated immune decision-making, promoting active immune responses against pathogenic organisms while favoring regulatory and tolerogenic pathways in response to commensal microorganisms. Through this selective immune sensing, oral tolerance contributes to the suppression of excessive or misdirected immune activation [166]. Experimental studies in animal models of autoimmune and inflammatory diseases, including type 1 diabetes, arthritis, experimental encephalomyelitis, and myasthenia gravis, have consistently demonstrated that induction of oral tolerance can attenuate a wide range of immune responses, underscoring its pivotal role in the preservation of peripheral immune homeostasis [167]. Given the importance of these functions to host health, loss of eubiosis at the host–microbiota interface is widely recognized as a central player to the development of chronic, age-related diseases [55,168].

In this context, plant-derived polyphenols have emerged as an important source of prebiotics, consumed either as raw dietary components or incorporated into functional foods and pharmaceutical preparations [169]. A substantial body of experimental evidence, particularly from animal models, supports the capacity of polyphenols to beneficially modulate both the GM and GALT, thereby mitigating pathological conditions. Table 2 synthesizes current evidence showing that polyphenol-induced changes in GM composition and function, together with immunomodulatory effects in the intestinal mucosa, parallel nutraceutical benefits across a range of autoimmune and chronic inflammatory diseases, including inflammatory bowel disease, type 1 diabetes mellitus, food allergies, obesity, type 2 diabetes mellitus and liver diseases.

6.1. Inflammatory bowel disease

A substantial body of *in vivo* evidence supports the therapeutic potential of polyphenols in inflammatory bowel disease (IBD), encompassing both ulcerative colitis (UC) and Crohn's disease (CD). These beneficial effects are increasingly attributed to the capacity of polyphenols to act as prebiotics, reversing disease-associated GM dysbiosis and restoring mucosal immune homeostasis, two hallmarks of IBD pathophysiology.

Among polyphenols, flavonoids are one of the most well-studied groups of phenolics in this context. Quercetin, for example, has exhibited the ability to ameliorate dextran sulfate sodium (DSS)-induced colitis in C57BL/6 J mice, administered at 10 mg/kg once every 3 days for 7 weeks, at least in part, by modulating the anti-inflammatory effects and bactericidal capacity of enteric macrophages [156]. Similarly, in BALB/c mice, dietary supplementation with 0.2% (w/w) nanoparticle curcumin promoted the expansion of butyrate-producing bacteria and increased SCFA levels in the feces, in parallel with elevated numbers of CD4$^+$ Foxp3$^+$ Treg and CD103$^+$ CD8α$^-$ regulatory DCs in the colonic mucosa [154], highlighting a functional link between microbial fermentation outputs and immune regulation. Berberine administration in DSS-induced colitis further supports a GM-dependent immunoregulatory mechanism. In this model, daily oral administration of 40 mg/kg of berberine for 7 days favorably modulated the Treg/Th17 balance; notably, this effect was abolished following GM depletion but restored by fecal transplantation from berberine-treated donors [177], demonstrating causality of microbiota-derived factors. Berberine-induced shifts in microbial composition included reductions in *Desulfovibrio* abundance and enrichment of the *Eubacterium* genus, underscoring the causal role of GM modulation in mediating immune outcomes. Likewise, treatment with the green tea flavonoid EGCG (50 mg/kg/day for 3 days) attenuated DSS-induced colitis in C57BL/6 mice and increased colonic SCFA concentrations [123]. Concurrently, EGCG supplementation reduced systemic levels of IL-8, IL-1β, IL-6, and TNF-α, with IL-6 and TNF-α also significantly decreased in colonic tissue, pointing to metabolite-mediated immunomodulation.

Beyond flavonoids, other polyphenolic subclasses, including quinic and hydroxycinnamic acids, have also exhibited protective effects in murine DSS-induced colitis. In particular, dietary supplementation with chlorogenic acid [155] and caffeic acid [178] (1 mM) alleviated colitis by suppressing colonic infiltration of F4/80$^+$ macrophages, CD3$^+$ T cells, and CD177$^+$ neutrophils through inhibition of the NF-κB signaling pathway. These effects were hypothesized to result from a polyphenol-driven increase in colonic *Akkermansia* abundance, further

Table 2
Polyphenol-induced changes in gut microbiota composition and function alongside their immunomodulatory and phytotherapeutic effects across a spectrum of metabolic, autoimmune and pro-inflammatory diseases.

	Model	Intervention	GM composition and function	Immunomodulatory activity	Phytotherapeutic effects	References
Obesity	HFD-fed C57BL/6 J mice	**Kaempferol** *0.1% in HFD for 16 weeks*	↓ Firmicutes/Bacteroidetes ↓ *Alistipes,* Lachnospiraceae_NK4A136_group, *Rombutsia, Faecalibacterium, Desulfovibrio, Helicobacter* ↑ *Akkermansia*	↓ Infiltration of colonic neutrophils, macrophages and DCs ↓ Colonic TNF-α, IL-6, IL-1β and MCP-1 mRNA and protein levels ↑ Colonic ZO-1, occludin and claudin-1 mRNA levels	↓ BW gain ↓ Fat accumulation ↓ Serum TC and TGs ↓ Plasma glucose levels	[153]
	HFD-fed Wistar rats	**Trans-resveratrol** *15 mg/kg/day added to the diet dissolved in ethanol for 6 weeks*	↓ *Erysipelotrichi* ↓ Gracaibacteraceae ↓ *Clostridium aldenense, Clostridium hathewayi, Clostridium sp. C9, Clostridium sp. MLG661, Parabacteroides distasonis, Gracilibacter thermotolerans* ↑ *Clostridium sp. XB90*	↑ Colonic TLR4 and IL-8 mRNA levels ↑ Colonic TJP-2 protein and occludin mRNA levels	↓ BW gain ↓ Fat accumulation ↑ Insulin sensitivity	[170]
	HFD-fed C57BL/6 J mice	**Grape polyphenols** (*Vitis labrusca* 'Concord') *10% in HFD for 13 weeks*	↓ Firmicutes/Bacteroidetes ↑ *Akkermansia muciniphila*	↑ Ileal occludin and proglucagon mRNA levels	↓ Hepatic lipid content ↑ Glucose tolerance ↓ Hepatic, intestinal, and plasmatic TGs ↓ Intestinal and hepatic inflammation ↓ Serum LPS	[171]
	HFHSD-fed C57BL/6 J mice	**American cranberry polyphenols** (*Vaccinium macrocarpon* Aiton) *200 mg/kg/day in HFHSD for 9 weeks*	↑ Eggerthellaceae ↑ *Akkermansia muciniphila, Parabacteroides goldsteinii*	↑ Colonic TLR2 and NLRP6 mRNA levels ↓ Colonic IL-1β mRNA levels ↑ Colonic GC number	↓ Visceral fat accumulation ↑ Glucose tolerance	[172]
Type 2 Diabetes Mellitus (T2DM)	HFHSD-fed C57BL/6 J mice	**Cranberry extract** (*Vaccinium macrocarpon* Aiton) *200 mg/kg/day via oral gavage for 8 weeks*	↑ *Akkermansia muciniphila*	↑ Colonic KLF4 and MUC2 mRNA	↓ BW gain ↓ Visceral fat accumulation ↓ Hepatic and plasmatic TGs ↓ Plasma TC ↓ Hepatic oxidative stress and inflammation ↑ Insulin sensitivity	[147]
	C57BLKS/J (−/−) (DB) mice	**Curcumin** *100 mg/kg/day orally dissolved in 1.5% (w/v) sodium carboxymethylcellulose for 21 days*	↑ *Candidatus saccharimonas, Eubacterium xylanophilum*	↓ Colonic cell infiltration ↓ Colonic IL-17A mRNA and protein levels ↓ Colonic BATF, C-Maf, RORγT and RORα mRNA levels ↓ MLNs Th17 ↑ MLNs Tregs	↑ Insulin sensitivity ↑ Glucose tolerance	[162]
Type 1 Diabetes Mellitus (T1DM)	NOD/LtJ mice	**Extra virgin olive oil** (Bellina®; *Olea europaea*) *2.5 mL/kg via oral gavage for 13 weeks*	↓ Firmicutes/Bacteroidetes ↑ *Lachnoclostridium, Ruminococcacae_UCG_005, Bacteroides, Muribaculum, Akkermansia*	↓ Colonic TNF-α and IL-6 protein levels ↓ PLNs integrin α4 and CCR9 protein levels ↓ Splenic Th1 cell number ↑ Splenic Th2 cell number	↓ Pancreatic inflammation ↓ Gastric emptying ↑ Glucose tolerance ↑ Insulin sensitivity	[173]
Liver Inflammation	LPS-induced hepatic inflammation in Sprague-Dawley rats	**Black chokeberry extract** (*Aronia melanocarpa 'Fu Kangyuan No. 1'*) *50, 100, 200 mg/kg/day via oral gavage for 4 weeks*	↓ Lachnospiraceae ↓ Actinobacteria, Verrucomicrobiota ↑ *Lactobacillus*	↓ Inflammatory cell infiltration in the colon and small intestine ↑ Small intestine ZO-1, occludin and claudin-1 protein levels	↓ BW gain ↓ Hepatic steatosis ↓ Hepatic inflammation and oxidative stress	[174]
Alcoholic Liver Disease (ALD)	Ethanol-induced ALD in ICR mice	**Zhenjiang vinegar extract** *800 mg/kg/day via oral gavage for 30 days*	↓ Firmicutes/Bacteroidetes ↑ *Verrucomicrobiota* ↓ Proteobacteria, Deferribacteres, Bilophila ↑ *Akkermansia,* Lachnospiraceae_NK4A136_group ↓ *Butyricimonas*	↓ Colonic immune cell infiltration ↑ Colonic IL-10, TGF-β, IL-22, Reg3b, Reg3g protein levels ↓ Colonic LPS, IL-6, IL-1β. TNF-α protein levels	↓ Liver weight ↓ Hepatic steatosis ↓ Hepatic inflammation and oxidative stress	[152]

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Table 2 (*continued*)

	Model	Intervention	GM composition and function	Immunomodulatory activity	Phytotherapeutic effects	References
Non-alcoholic Fatty Liver Disease (NAFLD)	High fructose-fed C57BL/6 J mice	**Loquat fruit extract** (*Eriobotrya japonica* (Thunb.) Lindl.) *25 and 50 mg/kg/day i.g for 8 weeks*	↓ Firmicutes/Bacteroidetes ↓ *Veilonella, Ruminiclostridium*	↑ Colonic ZO-1 and occludin mRNA and protein levels ↑ Colonic MUC2 and MUC4 mRNA levels ↓ Colonic TLR4, TLR5 and NF-κB mRNA levels ↑ Mucus area	↓ Liver weight ↓ BW gain ↓ Hepatic fat accumulation ↑ Glucose tolerance ↑ Insulin sensitivity ↓ Serum TC, LDL-C and TGs ↑ Serum HDL-C ↓ Hepatic inflammation and oxidative stress	[148]
	HFD-fed C57BL/6 J mice	**Sinapine** *500 mg/kg in rapeseed oil for 12 weeks*	↓ Firmicutes/Bacteroidetes ↑ Lactobacillaceae, Akkermansiaceae ↑ *Blautia*	↓ Colonic NF-κB and TNF-α mRNA levels ↑ Colonic GPR43 mRNA levels	↓ BW gain ↓ Visceral fat accumulation ↑ Glucose tolerance ↑ Insulin sensitivity ↓ Blood LDL-C ↓ Hepatic and adipose tissue inflammation	[175]
		Quercetin *0.05% (wt/wt) in the diet for 16 weeks*	↓ Firmicutes/Bacteroidetes ↓ Proteobacteria ↓ *Desulfovibrio, Helicobacter, Flavobacterium, Allobaculum, Suturella* ↑ *Akkermansia*	↑ Small intestine occludin and claudin-1 protein levels	↓ BW gain ↓ Visceral fat accumulation ↓ Liver weight ↓ Hepatic steatosis and inflammation ↑ Glucose tolerance ↑ Insulin sensitivity ↓ Plasma TGs	[176]
Inflammatory Bowel Disease (IBD)	Adoptive T cell transfer-induced colitis in Reg1$^{-/-}$ mice	**Quercetin** *10 mg/kg orally once every 3 days for 7 weeks*	↓ Firmicutes/Bacteroidetes ↓ Proteobacteria, Actinobacteria, Segmented filamentous bacteria ↓ *Escherichia coli*	↓ IFNγ^{+} and TNF-α^{+} CD4^{+} T cells in the colonic LP and MLNs ↓ Colonic TNF-α, IL-17A and IL-6 mRNA and protein levels ↑ Colonic IL-10 mRNA levels ↑ Mucosal wall thickness ↑ Colonic GC number ↑ Enteric M2 macrophage polarization	↓ Chronic intestinal inflammation	[156]
	DSS-induced colitis in BALB/c mice	**Curcumin** 0.2% (w/w) nanoparticle curcumin in the diet for 25 days	↑ *Clostridium cluster IV, Clostridium subcluster XIVa* ↑ Fecal butyrate	↓ Infiltration of colonic neutrophils ↑ Colonic DCs and Tregs numbers ↓ NF-κB activation in colonic epithelial cells ↓ Colonic TNF-α, IL-1β, IL.6, CXCL1, and CXCL2	↓ BW loss ↓ Disease activity index ↓ Colon edema ↓ Colonic inflammation	[154]
	DSS-induced colitis in BALB/c mice	**Berberine** *40 mg/kg/day orally diluted in drinking water for 10 days*	↑ *Eubacterium* ↓ *Desulfovibrio*	↓ Colonic IL-17 and RORγT mRNA levels ↑ Colonic IL-10 and Foxp3 mRNA levels ↓ Splenic Th17 cell number ↑ Splenic Treg cell number	↓ BW loss ↓ Disease activity index ↓ Colon shortening	[177]
	DSS-induced colitis in C57BL/6 mice	**Chlorogenic acid** *1 mM in the drinking water for 15 days* **Caffeic acid** *1 mM in the drinking water for 15 days*	↑ Firmicutes/Bacteroidetes ↑ Verrucomicrobiota ↑ *Akkermansia*	↓ Colonic infiltration of neutrophils, macrophages and CD3^{+} T cells ↑ Colonic mucin production	↓ Disease activity index ↓ Intestinal inflammation	[155] [178]
	TNBS-induced colitis in BALB/c mice	**Resveratrol** *100 mg/kg/day via oral gavage for 5 days*	↓ *Bacteroides acidifaciens* ↑ *Ruminococcus gnavus, Akkermansia muciniphila* ↑ Fecal butyrate	↑ Colonic GC number ↑ Mucus thickness ↑ MLNs CD4^{+} IL-10^{+} and Foxp3^{+} T cells ↓ MLNs CD4^{+} IFNγ^{+} and IL-17^{+} T cells	↓ BW loss ↓ Colon shortening ↓ Colonic inflammation	[163]
	T cell adoptive transfer-induced colitis in C57BL/6 J mice	**Aronia berry powder** (*Aronia melanocarpa 'Viking'*) 4.5% in the diet for 5 or 7 weeks	↓ *Akkermansia muciniphila, Bacteroides acidifaciens* ↑ *Ruminococcus gnavus*	↓ Colonic CD4^{+} T cell infiltration ↑ LP Treg cell numbers ↓ LP Th17 cell numbers	↓ BW loss ↓ Colon shortening ↓ Colonic inflammation	[157]

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Table 2 (*continued*)

	Model	Intervention	GM composition and function	Immunomodulatory activity	Phytotherapeutic effects	References
				↓ Colonic IFNγ and IL-6 mRNA levels		
	Winnie mice	**Bronze tomato** (Line *E8:MYB12, E8:Del/Ros, 35S:StSy*) *1% freeze-dried tomato in the diet for 2 weeks*	↑ *Akkermansia muciniphila* ↓ *Escherichia albertii, Parabacteroides distasonis, Ruminococcus gnavus, Bacteroides chinchila, Bacteroides rodentium, Bacteroides xylanisolvens*	↓ Colonic IFNγ mRNA levels ↑ Colonic IL-10 mRNA levels ↓ MLNs IFNγ and IL.17 A mRNA levels	↓ Colonic inflammation	[179]
	Oxazolone-induced intestinal inflammation in zebrafish	***Dendrobium candidum* fermentation liquid (FDC)** *0.15 g/L freeze-dried FDC in the water for 3 weeks*	↑ *Lactobacillus, Faecalibacterium, Rummeliibacillus* ↓ *Shewanella, Geodermatophilus, Peptostreptococcacea, Mycobacterium*	↓ Colonic cell infiltration ↓ Colonic IL-4 and TNF-α protein levels ↑ Colonic MUC2, ZO-1 and occludin protein levels	↓ Intestinal inflammation	[180]
Food Allergy	Ovalbumin-induced sensitization in BALB/c mice	**Cyanidin-3-O-glucoside** *25 mg/kg/day via oral gavage for 12 days*	↑ *Lactobacillus, Alistipes, Odoribacter* ↓ *Helicobacter, Turicibacter*	↑ Colonic ZO-1, occludin, claudin-1, IL-18, IL-10 and IL-22 protein levels ↓ Colonic TNF-α and IL-4 protein levels ↑ Colonic sIgA	↑ Motor activity ↓ Lethargy ↓ Shivering ↓ Diarrhea ↓ Anaphylactic score ↓ Inflammatory intestinal epithelial damage	[181]
		Extra virgin olive oil (Mueloliva®; *Olea europaea*) *1, 2 and 3 g/kg/day via oral gavage for 2 weeks pre-sensitization*	↓ Burkholderiaceae ↑ Clostridiaceae	↑ Ileal ZO-1, occludin, claudin-1, IL-22, IL-10, TGF-β1 and RegIIγ protein levels ↓ Ileal MUC2, IL-4, MCP-1 and TNF-α protein levels ↑ Ileal sIgA	↑ Body temperature ↓ Nasal scratching, convulsions and asthma	[151]

BATF – Basic Leucine Zipper ATF-Like Transcription Factor; **BW** – Body Weight; **C-Maf** – Cellular Musculoaponeurotic Fibrosarcoma; **CCR** – C-C Chemokine Receptor; **CXCL** – C-X-C Motif Chemokine Ligand; **DCs** – Dendritic Cells; **Foxp3** – Forkhead Box P3; **GC** – Goblet Cell; **GPR** – G-Protein-Coupled Receptor; **HDL.C** – High-density Lipoprotein Cholesterol; **IFNγ** – Interferon Gamma; **i.g.** – Intragastrically; **IL** – Interleukin; **KLF** – Krüppel-Like Factor; **LDL-C** – Low-density Lipoprotein Cholesterol; **LPS** – Lipopolysaccharide; **LP** – Lamina Propria; **MCP** – Monocyte Chemoattractant Protein; **MLNs** – Mesenteric Lymph Nodes; **MUC** – Mucin; **NLRP** – NOD-Like Receptor Pyrin Domain Containing; **NF-κB** – Nuclear Factor Kappa B; **PLN** – Pancreatic Lymph Nodes; **Reg** – Regenerating Islet-Derived Protein; **ROR** – Retinoid-Related Orphan Receptor; **sIgA** – Secretory Immunoglobulin A; **TC** – Total Cholesterol; **TG** – Triglycerides**; TGF-β** – Transforming Growth Factor Beta; **Th** – T Helper; **TJP** – Tight Junction Protein; **TLR** – Toll-Like Receptor; **TNF-α** – Tumor Necrosis Factor Alpha;; **Treg** – T Regulatory; **ZO** – Zonula Occludens

emphasizing the microbiota-mediated nature of their immunomodulatory action.

Resveratrol, a stilbene polyphenol, has likewise demonstrated potent microbiota-dependent immunoregulatory effects in trinitrobenzene sulfonic acid (TNBS)-induced colitis. Oral gavage of resveratrol (100 mg/kg), administered 24 h before TNBS injection and then daily for 5 days, increased the proportion of $CD4^+IL\text{-}10^+$ and $CD4^+$ $Foxp3^+$ T cells while reducing $CD4^+$ IFN-γ^+ and $CD4^+$ IL-17^+ T cell populations [163]. Simultaneously, TNBS-induced dysbiosis was reversed, with suppression of *B. acidifaciens* and enrichment of beneficial taxa such as *Ruminococcus gnavus* and *Akkermansia muciniphila*, alongside increased butyrate production. Crucially, these effects were transferable via fecal microbiota transplantation, supporting the notion that microbial metabolites drive T cell polarization. Likewise, a diet enriched with 4.5% (w/w) *Aronia* berry powder - an equivalent to a 70 kg adult consuming 1 cup of fresh aronia berries per day – for 5 or 7 weeks increased Treg frequencies in mesenteric lymph nodes and colonic tissue of colitic mice, an effect associated with enhanced microbial diversity [157]. Similarly, Winnie mice fed a diet containing 1% (w/w) bronze tomato displayed reduced IL-17A and IFN-γ production by MLNs T cells, accompanied by an increased abundance of *A. muciniphila* and decreased levels of *Bacteroides* spp., *Escherichia albertii*, *Parabacteroides distasonis*, and *R. gnavus* [179].

Interestingly, prebiotic efficacy of polyphenols in IBD extends beyond mammalian models. In zebrafish, fermented polyphenols derived from *Dendrobium candidum* (0.15 g/L for 3 weeks) significantly altered gut microbial composition by increasing *Lactobacillus*, *Faecalibacterium*, and *Rummeliibacillus*, while reducing *Shewanella*, *Geodermatophilus*, *Peptostreptococcaceae*, and *Mycobacterium* in a model of oxazolone-induced intestinal inflammation [180]. This microbial remodeling was accompanied by elevated intestinal SCFA levels and improved immune function, evidenced by reduced secretion of IL-10, IL-4, and TNF-α, reinforcing the central role of microbial metabolic cues in mediating host immune responses. Supporting this, daily oral administration of ellagic acid (50 mg/kg) for 7 days attenuated DSS-induced colitis in C57BL/6 mice, in association with reduced levels of pro-inflammatory cytokines in the colon (IL-1β, TNF-α, IL-6, IL-22), effects subsequently attributed to its microbiota-derived metabolite, UroA [58] 10.1038/s41419–023–06190–4. In addition, in LPS-stimulated Caco-2 epithelial cells, UroA improved barrier integrity by upregulating the expression of occluding, claudin-4 and ZO-1. Importantly, the protective effects of ellagic acid were lost upon GM depletion, thereby supporting a mechanism dependent on microbial biotransformation.

Collectively, these studies underscore the role of polyphenol-derived prebiotics as modulators of GM functionality, particularly metabolite production and related signaling pathways, thereby shaping mucosal immune tolerance in IBD. Despite this, several limitations in polyphenol research in IBD are acknowledged. Available data results mainly from animal studies, which often present significant variability (e.g., DSS-, TNBS-, oxazolone-induced colitis), alongside varied polyphenol dosing regimens. Moreover, the role of interindividual variability in microbial metabotypes remains largely unexplored, despite its likely impact on therapeutic response. Therefore, controlled clinical trials are warranted and future research should adopt a metabolomic perspective, as functional microbiome analyses will be critical to establish causal links between bacterial metabolism of polyphenols and clinical outcomes in IBD.

6.2. Type 1 diabetes mellitus

Although polyphenols have been extensively explored in T1DM management due to their anti-oxidant properties and their ability to modulate glucose, insulin, cholesterol, and triglyceride levels [182, 183], their impact on GM-immune system interactions in diabetic subjects has not been thoroughly investigated. Recent evidence, however, suggests that polyphenol-rich dietary interventions may exert prebiotic effects in T1DM through modulation of gut microbial metabolic activity and downstream immune signaling. In this context, daily administration of 2.5 mL/kg extra virgin olive oil (EVOO) via oral gavage from 7 to 20 weeks of age in NOD/LtJ mice demonstrated reduction of the Firmicutes-to-Bacteroidetes ratio and enhanced expansion of SCFA-producing bacteria, including *Ruminococcaceae_UCG-005* and *Lachnoclostridium* [173]. Importantly, these compositional shifts were paralleled by functional outcomes, including decreased colonic protein levels of the pro-inflammatory cytokines TNF-α and IL-6, consistent with enhanced SCFA-mediated immunoregulation. These effects occurred alongside downregulation of integrin α4 and CCR9 in pancreatic lymph nodes, indicative of reduced migration of gut-homing immune cells to pancreatic tissue. Moreover, EVOO administration contributed to the restoration of the Th1/Th2 balance in the spleen, highlighting its capacity to modulate systemic immune responses via gut-associated mechanisms. Similarly, Wistar rats with streptozotocin-induced T1DM consuming a diet supplemented with 10% *w/w* Corinthian currants, a rich source of phenolic compounds, for 4 weeks, decreased serum IL-1β levels in association with elevated fecal acetate levels [184], highlighting a GM-dependent immunomodulatory effect. In line with this, recent human data indicate that individuals with T1DM exhibit depletion of SCFA-producing bacteria, particularly *E. rectale*, accompanied by a severe reduction in microbial-derived phenolic metabolites, including gallic acid and related derivatives (e.g., 3,4-dihydroxyhydrocinnamic acid), with known anti-inflammatory and immunomodulatory properties [185]. This deficiency was linked to pancreatic beta cell function and islet autoimmunity, supporting the concept that microbial metabolite signatures may serve as functionally relevant biomarkers in the context of T1DM [186].

Although limited, these findings suggest that the immunoregulatory effects of polyphenol interventions in T1DM are mediated by changes in microbial functionality - particularly SCFA production - and associated immune signaling. Nevertheless, available evidence is largely restricted to animal models, with limited clinical data directly evaluating the impact of microbial metabolism in T1DM. In addition, most studies focus on GM compositional changes, while metabolic fluxes and causal links between bacterial metabolites and disease-modifying effects remain unexplored.

6.3. Food allergies

Plant-derived polyphenols exhibit notable anti-allergic properties and represent a promising reservoir for anti-allergy drug discovery and development [187,188]. Increasing evidence indicates that these effects are mediated not only by direct immunomodulatory actions but also by prebiotic-like mechanisms involving GM remodeling and restoration of mucosal immune tolerance-processes that are critically impaired in food allergy pathogenesis.

In this context, studies show that an olive oil-enriched diet is able to mitigate ovalbumin-induced food allergy in mice by restoring intestinal microecological balance [151,189]. Treatment repaired ileal morphology, upregulated TJ protein expression and enhanced epithelial barrier integrity. Functionaly, this is accompanied by a shift toward anti-inflammatory immune signaling, including increased production of Treg-associated cytokines such as IL-10 while suppressing Th2-associated immune mediators in the lamina propria [151,189]. These immunological improvements were accompanied by compositional shifts in the GM, characterized by a reduction in Burkholderiaceae and an increase in Clostridiaceae abundance [151]. Similarly, targeted colonic and rectal delivery of cyanidin-3-O-glucoside in the same murine model of food allergy normalized the Firmicutes-to-Bacteroides ratio, promoted beneficial genera such as *Lactobacillus* and *Odoribacter*, and inhibited pathogenic taxa including *Turicibacter* and *Helicobacter* [181], normalizing carbohydrate- and polyphenol-fermenting metabolic networks. These microbiota-driven changes coincided with strengthened intestinal epithelial barrier function, increased secretion of IgA and β-defensins, and restoration of Th1/Th2 immune balance, ultimately resulting in significant alleviation of allergic symptoms.

Despite the limited number of studies directly evaluating the effects of microbial-derived phenolic metabolites on food allergy models, growing evidence supports their role in modulating key allergy-related mechanisms. For instance, the ellagitannin-derived metabolite urolithin A has been shown to suppress IgE-mediated degranulation in the RBL-2H3 rat basophil cell line through concentration-dependent inhibition of Akt phosphorylation (2–10 μM) [190]. A similar effect was observed after a short pre-incubation of RBL-2H3 cells with the isoflavone-derived metabolite equol [191]. Moreover, equol attenuated the expression of CD63 - a marker of basophil activation - reinforcing the anti-allergic potential of these microbiota-derived metabolites.

Taken together, available studies indicate that the anti-allergic effects of polyphenols are mediated primarily by GM-dependent mechanisms that regulate intestinal barrier integrity and immune tolerance. Despite these advances, the field is still dominated by evidence from *in vitro* and animal studies, with scarce clinical data linking specific metabotypes or metabolite profiles to allergy outcomes. The heterogeneity of experimental models and allergen variety further difficult cross-study comparability. Future investigations should prioritize human intervention studies incorporating metabolomic profiling to establish causal relationships between microbial metabolism of polyphenols and modulation of allergic disease.

6.4. Obesity

Polyphenolic supplementation has been widely applied as a nutraceutical strategy in obesity, particularly due to the capacity of plant-derived polyphenols to act as prebiotic-like compounds that modulate GM composition and function. Through selective interactions with intestinal microbial communities, polyphenols contribute to the restoration of eubiosis, reinforcement of epithelial barrier integrity, and regulation of mucosal immune responses, all of which are critically disrupted in obesity-associated metabolic inflammation.

Among polyphenols, flavonoids represent one of the most intensively studied classes in the context of obesity and its related metabolic disturbances. Bian *et al.* demonstrated that dietary supplementation with kaempferol (0.1% w/w) attenuated HFD-induced metabolic dysfunction in mice including excessive fat accumulation, glucose intolerance, and adipose tissue inflammation [153]. Importantly, kaempferol improved intestinal barrier function and attenuated gut inflammation by limiting the infiltration of neutrophils, macrophages, and DCs, as well as suppressing the expression of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, and monocyte chemoattractant protein-1(MCP-1). These beneficial effects were strongly associated with kaempferol's ability to counteract obesity-induced gut dysbiosis, highlighting its prebiotic-like role in reshaping the microbial ecosystem and downstream immune responses.

Consistent with this concept, a study evaluating the combined supplementation with quercetin (30 mg/kg/day) and trans-resveratrol (15 mg/kg/day) in obese Wistar rats revealed that trans-resveratrol alone or in combination significantly upregulated in the expression levels of TJ protein-2 and occludin gene, whereas quercetin alone showed limited effects [170]. Furthermore, trans-resveratrol induced the expression of TLRs and IL-18, which are essential for maintaining epithelial integrity and preventing bacterial translocation. The authors suggested that trans-resveratrol promotes intestinal epithelial repair

through microbiota-driven activation of TLR signaling pathways, leading to IL-18-mediated protective responses. This mechanism exemplifies how polyphenol-derived metabolites can elicit controlled immune activation that supports mucosal homeostasis rather than exacerbating inflammation. Accordingly, GM-derived 4-hydroxyphenylacetic acid from resveratrol supplementation has been shown to reverse obesity and glucose intolerance in HFD-fed mice through activation of sirtuin-1 (SIRT-1) signaling [192], highlighting a direct metabolite-driven mechanism linking microbial activity to host metabolic regulation.

Analogous prebiotic effects have been reported for grape polyphenols, which have been shown to beneficially remodel gut microbial communities, suppress intestinal and systemic inflammation, and improve metabolic outcomes in obese models [171]. In HFD-fed C57BL/6 J mice, supplementation with 1% grape polyphenols reduced triglyceride storage and increased intestinal expression of genes involved in barrier function, such as occludin, as well as proglucagon [171]. Moreover, supplementation with grape polyphenols significantly increased the abundance of *A. muciniphila* while reducing the proportion of Firmicutes to Bacteroidetes, a microbial signature typically associated with resistance to diet-induced obesity.

In line with these findings, a study performed by Medina-Larqué *et al.* evaluating the anti-obesogenic properties of cranberry polyphenols (CPs) and agave agavins (AGs) in mice demonstrated that these plant-derived compounds exert complementary prebiotic actions on gut composition and immune regulation [172]. The equivalent of 100 g of fresh fruit and 5 g/day in humans of CPs (200 mg/kg) and AGs (1 g/kg), administered alone or in combination with CPs for 9 weeks, increased bacterial fermentation activity and elevated SCFA production, particularly butyrate, alongside modulation of immune cues. Specifically, both compounds promoted Tlr2 expression and decreased IL-1β expression, while AGs selectively induced Foxp3 expression, suggesting the promotion of regulatory immune pathways linked to microbiota-derived metabolites [172]. Aligning with this framework, an ongoing clinical trial (NCT05432362) involving obese women with depression is aiming to evaluate the effects of consuming 200 mL of a commercially-available *Aronia melanocarpa* juice in addition to their regular diet on Treg cell numbers [193].

Emerging clinical evidence further reinforces the therapeutic role of GM-mediated polyphenol metabolism in the context of obesity. González-Sarrías *et al.* reported that obese individuals with distinct urolithin metabotypes experienced differential metabolic outcomes following consumption of an ellagitannin-rich pomegranate extract for 3 weeks (640 mg phenolics/day) [194]. Improved blood lipids profiles were observed only in individuals classified as UM-B, with these effects partially correlating with urolithin production and increased Gordonibacter levels. Notably, these individuals also presented higher baseline cardiovascular risk, which may have contributed to the magnitude of the observed response, highlighting the need for cautious interpretation and further investigation. Complementary evidence from an acute dietary intervention further supports a metabolite-driven mechanism. A study involving 10 healthy males which consumed physiologically achievable doses of red raspberries (200 g and 400 g, providing 201 and 403 mg total polyphenols, respectively) reported significant improvements in endothelial function, as assessed by flow-mediated dilation [195]. Importantly, the vascular benefits were positively correlated with circulating levels of urolithin A-sulfate and urolithin A-3-glucuronide, pointing to microbial-derived metabolites as direct contributors to vascular responses following polyphenol intake.

Collectively, these findings indicate that interindividual variability in microbial metabolic capacity may influence polyphenol-mediated anti-obesogenic effects. However, the limited number of clinical studies, small sample sizes, and variability in baseline metabolic status underscore the need for larger, stratified trials to clarify the role of metabotypes in modulating obesity-related outcomes.

6.5. Type 2 diabetes mellitus

In line with findings reported by Medina-Larqué *et al.*, cranberry supplementation has also been evaluated as a polyphenol-based phytotherapeutic strategy in mice with high fat/high sucrose (HFHS)-induced type 2 diabetes mellitus (T2DM) [147]. Administration of 200 mg/kg/day of a cranberry extract for 8weeks was associated with increased expression of Kruppel-like factor 4 (Klf4), a marker of goblet cell differentiation, as well as elevated Muc2 mRNA levels. These changes contributed to the establishment of a mucus-rich ecological niche that favored the expansion of *Akkermansia* spp., a bacterium widely recognized for its prebiotic responsiveness and metabolic benefits.

Beyond cranberries, curcumin has also been investigated as a polyphenol-derived prebiotic in T2DM, particularly in the context of intestinal inflammation. In diabetic mice with colitis, curcumin administration (100 mg/kg/day) significantly alleviated diabetic symptoms, reduced mucosal inflammatory cell infiltration, and promoted a shift towards weaker Th17 and stronger Treg responses [162]. In addition, curcumin supplementation modulated intestinal bacterial diversity and abundance, indicating that its therapeutic effects were, at least in part, mediated through restoration of GM composition and Th17/Treg balance.

Notably, accumulating evidence supports a central role for microbial-derived metabolites in mediating the anti-diabetic effects polyphenols. For example, administration of 3,4-dihydroxyphenylacetic acid (DHAA), a microbial catabolite of dietary polyphenols, at 75 or 150 mg/kg/day for 4 weeks attenuated systemic inflammation in mice with streptozotocin-induced T2DM, as demonstrated by reduced circulating levels of LPS and IL-6 and increased IL-10 [43]. In parallel, DHAA improved gut barrier function by enhancing TJ protein expression and inhibiting the MAPK-MLCK signaling pathway in the colon [43], indicating a direct role in maintaining epithelial homeostasis. Consistent with these findings, a clinical study with 7 T2DM patients further demonstrated that consumption of red raspberry (123 g/day) for 2 weeks led to significant reductions in high sensitivity CRP and a trend for reduced insulin resistance, in association with increased circulating levels of microbial metabolite, particularly urolithin conjugates including urolithin A glucuronide and urolithin A sulphate, as well as PCA and 3,4-dihydroxyphenylacetic acid [196], reinforcing metabolite-mediated mechanisms underlying the anti-diabetic effects of polyphenols.

Overall, these findings support the concept that polyphenol-derived compounds exert prebiotic-like effects in T2DM primarily driven by microbiota-dependent functional outputs, including enhanced production of bioactive metabolites, reinforcement of the mucus and epithelial barrier, and modulation of inflammatory and metabolic signaling pathways. Nevertheless, evidence from well-controlled human studies is still limited. Significant variability in polyphenol sources, dosing regimens, and dietary contexts further complicates direct comparisons across studies. In addition, individual differences in microbial metabotypes are rarely accounted for, despite their influence on metabolic responses. Therefore, future research should focus on stratifying participants by metabotype, quantifying metabolite production, and establishing causal pathways through controlled clinical interventions.

6.6. Liver diseases

Polyphenols have been widely reported to ameliorate liver pathologies, traditionally attributed to their local antioxidant, anti-inflammatory, and metabolic-regulatory properties [197,198]. However, growing evidence implicates GM dysbiosis as a central contributor to liver disease pathogenesis, giving rise to the emerging concept of the gut–liver axis [199,200]. Within this framework, impairment of the mucosal immune system can promote dysbiosis and bacterial translocation, thereby accelerating liver disease progression [199–201].

In this context, polyphenols have emerged as modulators of microbiota-dependent immune and barrier functions. For example, dietary supplementation with 0.4% dietary green tea EGCG (w/w) for 14 weeks prevented HFD-induced liver disease onset in C57BL/6 mice, in association with marked improvements in intestinal mucosal immunity [202]. Diseased animals exhibited elevated ileal macrophages and dendritic cells' (DCs) expression of cluster of differentiation 11b (CD11b), μ11c, CD80, CD86, CD163, and major histocompatibility complex class II (MHC-II), alongside increased levels of B-cell activating factor (BAFF) and TGF-β, molecules involved in antigen presentation and B-cell differentiation, which were effectively reversed by EGCG supplementation.

Similarly, a polyphenol-rich extract of *Aronia melanocarpa* improved intestinal barrier integrity by upregulating the expression of ZO-1, occludin, and claudin-1 in the small intestine of a LPS-induced liver disease rat model in a dose-dependent manner [174]. In parallel, this intervention reshaped GM composition by reversing disease-associated overgrowth of Actinobacteria and Verrucomicrobiota genera while increasing the abundance of commensal Lactobacillus. Together, these findings suggest that *A. melanocarpa* polyphenols may exert hepatoprotective effects through coordinated reinforcement of epithelial defenses and restoration of microbial balance along the gut–liver axis.

6.6.1. Alcohol-related liver disease

The prebiotic potential of polyphenols has been further demonstrated in alcohol-related liver disease (ALD). In a murine model of ALD, supplementation with Zhenjiang aromatic vinegar extract (200 and 800 mg/kg/day for 30 days) restored intestinal homeostasis at both histological and molecular levels [152]. Treatment markedly reduced colonic immune cell infiltration and crypt atrophy, while enhancing the expression of anti-inflammatory cytokines (IL-10, IL-22, transforming growth factor beta 1 (TGF-β1)) and antimicrobial peptides [regenerating islet-derived proteins 3b (Reg3b) and Reg3g)]. Concurrently, the expression of pro-inflammatory cytokines, including IL-6, IL-1β, and TNF-α, was significantly suppressed. These immunological improvements were accompanied by pronounced remodeling of GM composition, characterized by a reduced Firmicutes-to-Bacteroidetes ratio, decreased abundance of Proteobacteria and Deferribacteres, and increased Verrucomicrobiota. At the genus level, enrichment of Akkermansia and Lachnospiraceae_NK4A136_group was observed, whereas Bilophila and Butyricimonas were depleted. Indeed, supplementation was associated with decreased hepatic levels of LPS and reduced activation of TLR4, key drivers of endotoxemia-induced liver inflammation, reflecting a shift in GM activity toward reduced endotoxin production. These findings highlight a microbiota-dependent mechanism through which polyphenols may attenuate endotoxemia-driven liver inflammation.

6.6.2. Non-alcoholic fatty liver disease

Evidence supporting the prebiotic role of polyphenols in non-alcoholic fatty liver disease (NAFLD) has primarily emerged from studies employing HFD and/or high-fructose diet–induced mouse models. For instance, a polyphenol-rich loquat fruit extract administered intragastrically at 25 and 50 mg/kg/day significantly improved fructose-induced intestinal barrier disruption by modulating TJ proteins (ZO-1 and occludin) and mucin expression in the colon of C57BL/6 J mice, while concurrently normalizing the colonic Firmicutes-to-Bacteroidetes ratio and reducing the relative abundance of *Veillonella*, ultimately attenuating liver injury [148]. Comparable microbiota-modulating effects were reported in HFD-induced NAFLD mice supplemented with sinapine, a rapeseed-derived polyphenol, at 500 mg/kg for 12 weeks. These changes were associated with suppression of NF-κB signaling and enhanced SCFA-mediated G-protein coupled receptor 43 (GPR43) expression, potentially driven by the expansion of beneficial microbial taxa such as Lactobacillaceae, Akkermansiaceae, and Blautia [175]. Consistent with these findings, dietary supplementation with quercetin (0.05% wt/wt) protected C57BL/6 mice against NAFLD-associated gut-liver dysfunction by increasing SCFA production and upregulating TJ proteins such as ZO-1 and occludin in the small intestine [176].

Collectively, studies exploring polyphenol supplementation in liver disease converge on a shared mechanism centered on modulation of the gut–liver axis through microbiota-dependent functional outputs. Across NAFLD and ALD models, consistent findings include reinforcement of intestinal barrier integrity, reduction of endotoxemia, and attenuation of hepatic inflammation. These effects are frequently associated with increased production of microbiota-derived metabolites, such SCFAs and phenolic derivatives, which contribute to epithelial homeostasis and immune regulation. Despite this convergence, the strength of evidence remains unstable. Most data are derived from rodent models, with limited clinical validation. Additionally, many studies infer functional changes from GM compositional shifts without directly measuring metabolite production or microbial enzymatic activity. Variability in disease models (e.g., HFD, alcohol, LPS-induced) and polyphenol formulations further complicates interpretation, and the contribution of individual metabotypes to liver disease outcomes remains poorly characterized. Future work should prioritize human studies integrating metabolomics to establish causal links between microbial metabolism of polyphenols and hepatoprotection.

7. Conclusions and future directions

Polyphenols have traditionally been described as *prebiotic-like* compounds, reflecting the ongoing debate regarding their formal classification as prebiotics. Nevertheless, accumulating evidence increasingly supports their conceptual reframing as *next-generation* prebiotics, since their overall effects on gut microbiota ecology, integrating both classical prebiotic actions *sensu stricto* and selective antimicrobial activities, appear to exceed the sum of these individual mechanisms. Although many studies continue to ascribe prebiotic properties to polyphenols based primarily on the stimulation of beneficial intestinal symbionts, often without experimentally demonstrating their direct utilization by the gut microbiota, a growing number of investigations now provide mechanistic evidence that aligns polyphenols with ISAPP contemporary framework. Importantly, the revised ISAPP definition prioritizes biological function over chemical class, recognizes non-carbohydrate substrates, and explicitly accommodates context-dependent, microbiota-mediated mechanisms of action. Within this perspective, the intrinsically low bioavailability of most dietary polyphenols, historically regarded as a pharmacokinetic limitation, emerges instead as a defining functional advantage. Because a substantial proportion of ingested polyphenols escapes absorption in the small intestine, these compounds reach the colon at biologically relevant concentrations, where they remain available for selective microbial utilization *in situ*. Their colonic persistence maximizes interactions with the gut microbiota and gut-associated lymphoid tissue, enabling sustained modulation of microbial ecology, epithelial barrier integrity, and mucosal immune homeostasis. Accordingly, poor systemic absorption should not be viewed as a drawback, but rather as a prerequisite for prebiotic bioactivity, ensuring that polyphenols exert their effects precisely where host-microbiota crosstalk is most intense.

Importantly, the prebiotic functionality of polyphenols extends well beyond the selective stimulation of beneficial taxa, encompassing a coordinated network of direct and indirect actions within the intestinal ecosystem. Polyphenols exert selective antimicrobial pressure against pathobionts while simultaneously favoring commensal and metabolically advantageous microorganisms, a phenomenon referred to as a *duplibiotic* effect, thereby contributing to ecological selectivity within the gut microbiome. These effects are further amplified through extensive microbial biotransformation, a central pillar of polyphenol functionality, whereby gut microorganisms harboring specialized enzymatic machinery convert structurally complex parent compounds into a

diverse repertoire of low-molecular-weight phenolic metabolites. Notably, these metabolites may retain, enhance, or diversify the bioactivity of their precursors, thus fulfilling the criteria of *bona fide* postbiotics. Acting locally, they reinforce epithelial barrier function, promote immune tolerance, and modulate inflammatory signaling, while a proportion also reaches distal organs to mediate systemic physiological effects. Simultaneously, both native polyphenols and their microbial-derived metabolites directly interact with intestinal epithelial and mucosal immune cells, acting as mild physiological stressors capable of activating endogenous cytoprotective and immunoregulatory pathways, in accordance with mechanisms associated with trained immunity [203,204]. Importantly, these host-directed actions do not weaken the rationale for considering polyphenols within the prebiotic framework; rather, they reinforce it, in line with the 2024 ISAPP recognition that health benefits may arise from integrated microbiota–host interactions, and not exclusively from shifts in microbial composition alone.

Beyond the generation of phenolic metabolites, polyphenols also reprogram microbial metabolism**,** shifting bacterial function toward a more symbiotic phenotype. This includes enhancement of SCFAs biosynthesis**,** a cornerstone of mucosal immune regulation, as well as modulation of BEVs production and cargo composition. SCFAs and BEVs represent additional, highly bioactive classes of postbiotics that function as molecular messengers between the microbiota and the host. Through these mechanisms, polyphenols indirectly expand the postbiotic landscape, reinforcing their immunomodulatory effects across distinct intestinal mucosal compartments, namely the epithelial barrier, lamina propria, Peyer's patches as well as mesenteric lymph nodes. The capacity of BEVs to cross the intestinal barrier further provides a mechanistic basis for the extra-intestinal effects of polyphenols**.** Collectively, these layered effects illustrate that polyphenols do not operate through a single prebiotic pathway but rather expand the functional repertoire of carbohydrate-based prebiotic activity currently being explored across a broad spectrum of autoimmune and inflammatory conditions, including inflammatory bowel disease, diabetes and food allergies, to name a few. Notably, the biological outcomes of these processes are shaped by microbial metabotypes**,** which define an individual's capacity to convert specific polyphenols into bioactive metabolites. Metabotypes therefore represent a key determinant of interindividual variability in responsiveness to polyphenol-based interventions. While this variability poses challenges for clinical translation, it simultaneously highlights the potential of polyphenols as tools in precision immunonutrition protocols, where interventions are tailored to individual microbial functionality and mucosal immune phenotypes in accordance with individual requirements, health status and metabolic variability.

Despite this promise, evidence regarding the prebiotic effects of polyphenols remains limited namely due to substantial methodological heterogeneity across studies. Differences in substrate characterization, inoculum origin, fermentation models, dosage, and analytical approaches strongly influence microbial outcomes and hinder the direct comparison and reproducibility of results. Although *in vitro* and *in vivo* studies frequently report beneficial modulation of gut microbiota composition, increased short-chain fatty acid production, and improvements in intestinal and metabolic parameters, inconsistencies in experimental design and reporting continue to limit the translational relevance of these findings and the establishment of robust cause-effect relationships. In addition, the chemical diversity of polyphenols, their non-linear dose–response relationships, and their dependence on food matrix and host-related factors (*e.g.* age, sex, metabolic and immune status) complicate standardization and cross-study comparisons [205–207]. Moreover, processing methods and formulation strategies can substantially influence polyphenol bioavailability and colonic delivery, contributing to discrepancies between the effects of isolated compounds and whole-food interventions [208–211]. These challenges are compounded by the current lack of robust, clinically applicable biomarkers to guide intervention design, together with regulatory constraints on health claim validation, both of which are essential for the clinical translation of well-defined polyphenol-based prebiotic protocols. Such limitations underscore the need for integrative multi-omics approaches and well-controlled human intervention studies to establish causality and refine health claims. Addressing these issues will be essential to fully harness the translational potential of polyphenols-based prebiotics in the development of nutraceuticals and functional foods targeting intestinal mucosal immune responses.

CRediT authorship contribution statement

Sofia Viana: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Flávio Reis:** Writing – review & editing, Validation, Supervision, Resources, Formal analysis. **Maria Manuela Pintado:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Lígia Salgueiro:** Methodology, Investigation, Formal analysis. **Miguel Castelo Branco:** Writing – review & editing, Validation, Supervision, Formal analysis. **João Malva:** Writing – review & editing, Resources, Methodology, Investigation, Formal analysis. **Artur Figueirinha:** Methodology, Investigation, Formal analysis. **Pedro Vieira:** Methodology, Investigation. **Carolina Ferreira:** Writing – original draft, Methodology, Investigation, Data curation.

Declaration of Generative AI and AI-assisted technologies in the writing process

AI-assisted technologies, namely ChatGPT (GPT-4.0), was employed solely to improve English language fluency and readability in sections of the manuscript. All modifications were carried out under human supervision, with the authors carefully reviewing and editing the content. Authors take full responsibility for the content of the published article.

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Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any comercial, financial or scientific relationships that could be construed as a potential conflict of interest.

Data availability

No data was used for the research described in the article.

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