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Review

Polyphenols Bioactive Metabolites, and Their Anti-Biofilm and Neuroprotective Potential

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Abstract

Polyphenols are widely studied phytochemicals with well-known antioxidant and anti-inflammatory properties. They are commonly present in fruits, vegetables, and plant-based foods. Beyond these classical roles, growing evidence shows that polyphenol-derived bioactive metabolites—produced or modified by the gut microbiota—can promote host health. These metabolites are increasingly recognized for shaping host–microbe interactions and influencing neurophysiological functions via the gut–brain axis. This review provides an overview of polyphenol transformation rates by the gut microbiome, highlighting their microbial transformation, anti-biofilm effects, and neuroprotective potential. In our opinion, a deeper understanding of the properties of these metabolites can significantly impact food science and biotechnology.

Keywords: polyphenols; gut microbiome; biofilm; quorum sensing; neurodegenerative diseases; neuroprotection

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1. Introduction

The human gut microbiota plays a crucial role in host physiology by transforming dietary components into bioactive molecules. Among these, polyphenols are a diverse class of secondary plant metabolites with well-documented antioxidant and anti-inflammatory properties [1]. Increasingly, they are being re-evaluated in the context of host–microbe interactions, which broadens the understanding of their biological significance.

Because polyphenols are poorly absorbed in the upper gastrointestinal tract, they reach the colon largely intact, where they undergo extensive microbial transformation [2]. This process generates low-molecular-weight phenolic metabolites, such as phenolic acids, urolithins, and valeric acids, which often exhibit greater bioactivity and bioavailability than their parent compounds [3]. These metabolites serve as key mediators in the diet–microbiota–host axis, influencing immune, metabolic, and neurological pathways [4,5].

Recent studies highlight their potential as anti-biofilm agents that can attenuate pathogen virulence without promoting antimicrobial resistance [6,7]. Moreover, their

ability to modulate the gut–brain axis suggests a role in neuroprotection and the prevention of neurodegenerative diseases such as Alzheimer's and Parkinson's [8,9]. This review explores the microbial metabolism of polyphenols, the resulting bioactive metabolites, and their mechanistic roles, with a focus on anti-biofilm and neuroprotective potential. Such information could help design microbiota-friendly foods, including prebiotics, synbiotics, and polyphenol-rich formulations relevant to human health and applied food microbiology.

2. Polyphenols: Chemical Classification and Dietary Sources

2.1. Chemical Classification of Polyphenols

Polyphenols are chemically heterogeneous plant metabolites defined by one or more aromatic rings with hydroxyl groups (Figure 1). This structural framework underlies their antioxidant activity and their interactions with enzymes, receptors, and microbial communities [6]. Dietary polyphenols are generally classified into phenolic acids, flavonoids, stilbenes, lignans, and tannins [10]. This classification is key to understanding their physicochemical properties, metabolic fate, and health effects (Table 1).

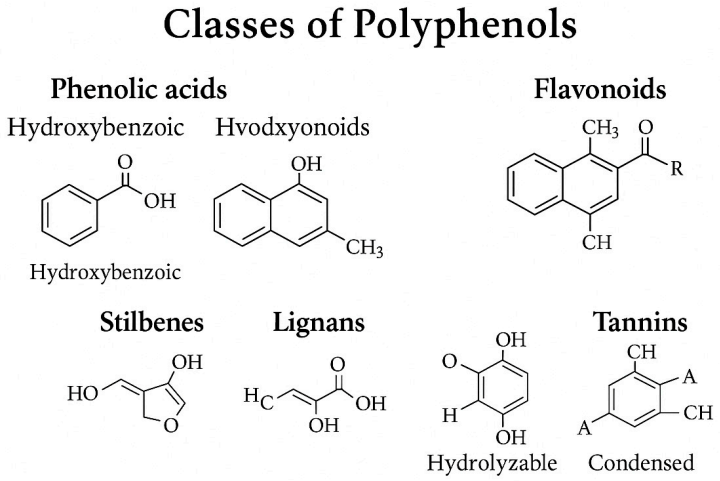

Figure 1. Molecular structure of the main classes of polyphenols.

Table 1. Main classes of dietary polyphenols: representative compounds, food sources, and key features.

Polyphenol Class	Representative Compounds	Main Dietary Sources	Key Features
Phenolic acids	gallic acid, protocatechuic acid, caffeic acid, ferulic acid	berries, coffee, tea, whole grains, olives	Widely distributed in plants; precursors of many microbial metabolites [11]
Flavonoids	quercetin, catechins (EGCG), naringenin, hesperetin, anthocyanins	fruits (apples, berries, citrus), vegetables, tea, cocoa, red wine	Largest subclass; diverse structures and bioactivities [12]
Stilbenes	resveratrol, piceatannol	grapes, red wine, peanuts, berries	Known for their antioxidant and neuroprotective effects [13]
Lignans	secoisolariciresinol, matairesinol, enterolactone	flaxseed, sesame, whole grains, and vegetables	Converted by gut microbiota into enterolignans [14]
Tannins (hydrolyzable & condensed)	ellagitannins, proanthocyanidins	Nuts, berries, pomegranate, tea, wine	High molecular weight; precursors of urolithins and valerolactones [15]

2.1.1. Phenolic Acids

Phenolic acids comprise two primary subclasses: hydroxybenzoic acids, which contain seven carbon atoms, and hydroxycinnamic acids, which contain nine carbon atoms [16].

Specifically, the derivatives of benzoic acid—including gallic, p-hydroxybenzoic, protocatechuic, salicylic, and ellagic acids—serve as antioxidant and antimicrobial agents in plants. In contrast, the derivatives of cinnamic acid—including *p*-coumaric, caffeic, and ferulic acids—act as intermediates in plant metabolic pathways. These compounds are commonly found in berries, coffee, tea, and whole grains, where they often exist as esters or glycosides. Notably, they are typically small, water-soluble molecules that undergo relatively rapid microbial metabolism in the colon, resulting in bioactive derivatives such as di-hydroxy-phenyl-propionic and phenylacetic acids.

2.1.2. Flavonoids

Flavonoids are the largest and most diverse group of polyphenolic compounds found in our diet, with over 6000 types identified in nature. All flavonoids share a basic structure consisting of two six-carbon rings (the A and B rings) joined by a three-carbon link, which usually forms a third, central ring (the C ring). This similar structure allows flavonoids to be grouped into subclasses based on small chemical changes in the central ring. Each type has different features based on how the rings gain or lose small chemical groups, such as sugars, hydroxyl, or methyl groups. Examples of common flavonoids include quercetin, catechin, naringenin, cyanidin–glycoside, and daidzein. Flavonoids can be found as pure compounds or attached to sugars and other molecules. These compounds give fruits, vegetables, herbs, and spices their colours and are also known as dietary supplements that help support health and prevent diseases (10,17). Table 2 shows the main flavonoid subclasses.

Table 2. Main flavonoid subclasses, including the key biological activities, bioavailability, and metabolism.

Flavonoid Subclass	Representative Compounds	Main Dietary Sources	Key Biological Activities	Bioavailability and Metabolism
Flavonols	Quercetin, Kaempferol	Onions, kale, apples, berries	Potent antioxidant and anti-inflammatory effects	Mostly occur as glycosides; poorly absorbed in the small intestine but extensively metabolized by gut microbiota into bioactive phenolic acids.
Flavones	Luteolin, Apigenin	Parsley, celery, chamomile	Anti-cancer and neuroprotective properties	Undergo microbial deconjugation and transformation into more minor phenolic metabolites with enhanced bioactivity.
Flavanones	Naringenin, Hesperetin	*Citrus* fruits (oranges, grapefruits)	Vascular protection, antioxidant, and anti-inflammatory effects	Microbial metabolism yields phenylpropionic and phenylacetic acids, which support cardiovascular health.
Flavanols (Catechins)	Epicatechin, Epigallocatechin gallate (EGCG)	Tea (especially green tea), cocoa, grapes	Modulation of gut microbiota; cardiovascular and metabolic benefits	Converted into valerolactones and hydroxyphenylvaleric acids by colonic microbiota, and exhibit improved absorption and stability.
Anthocyanins	Cyanidin, Delphinidin	Berries, grapes, red cabbage, eggplants	Anti-inflammatory, anti-diabetic, neuroprotective activities	Rapidly degraded by gut microbiota to produce phenolic acids with preserved bioactivity.
Isoflavones	Genistein, Daidzein	Soybeans, legumes	Estrogenic, anti-osteoporotic, and cardioprotective effects	Act as phytoestrogens; metabolized by intestinal bacteria (e.g., into equol) with enhanced bioavailability and selective estrogen receptor modulation.

2.1.3. Stilbenes

Stilbenes are non-flavonoid polyphenols made of two phenyl rings (A and B) linked by a two-carbon ethylene bridge. They occur as cis or trans isomers and may be free or glycosylated compounds [17]. The A ring usually has two meta-oriented hydroxyl groups. The B ring shows variable hydroxyl or methoxy substitutions. In plants, stilbenes are synthesized as a defence mechanism against pathogens, mainly through the phenylpropanoid pathway. Resveratrol (3,5,4′-trihydroxystilbene) is the most studied of these compounds. It is found in grapes, berries, and peanuts [16]. Resveratrol is abundant in red wine; both it and its microbial metabolites (such as dihydroresveratrol) have strong antioxidant and neuroprotective properties. These properties may lower the risk of cardiovascular and neoplastic diseases [10,18].

2.1.4. Lignans

Lignans are non-flavonoid polyphenols formed by the dimerization of two C6–C3 phenylpropanoid units via a β–β-β′(8–8′) bond. Their structural diversity, due to varied C9 substitutions, gives rise to several subtypes, including furan, dibenzylbutane, and dibenzylbutyrolactone derivatives [19]. Found mainly in legumes, oilseeds (e.g., flaxseed and sesame), and whole grains, lignans occur primarily in the aglycone form. Dietary lignans show antioxidant, estrogenic, and chemopreventive properties [10]. Notably, secoisolariciresinol diglucoside (SDG) is metabolized by gut microbes into enterolignans—specifically, enterodiol and enterolactone—which exhibit phytoestrogenic, anti-inflammatory, and cardioprotective effects, particularly in hormone-dependent cancers [10,19].

2.1.5. Tannins

Tannins are large plant compounds (weighing around 500 to 30,000 Daltons) and come in two main types: condensed and hydrolysable. Condensed tannins are composed of repeated units, such as catechin and epicatechin. A-type tannins have a mix of bonds, while B-type tannins only have strong bonds, making them hard to break down except by gut microbes. Hydrolysable tannins are made when gallic or ellagic acid joins to sugar, forming gallotannins and ellagitannins. Tannins are commonly found in fruits, grains, beans, tea, and wine, where they help protect plants and offer humans antioxidant and anti-inflammatory benefits.

2.2. Factors Affecting Polyphenol Content

Genetic, environmental, and technological factors shape the polyphenol content of foods. These factors influence not only concentration but also composition, stability, and bioavailability (Table 3). Post-harvest and processing steps—such as drying, roasting, fermentation, or mechanical disruption—can trigger chemical changes. Sometimes these transformations enhance bioactivity [20,21]. Ripeness and harvest timing alter the balance among anthocyanins, flavonols, and tannins. Agronomic and environmental conditions, such as UV exposure, soil composition, and altitude, regulate phenolic biosynthesis through the phenylpropanoid pathway [22–25]. These variables ultimately affect the availability of polyphenols as substrates for microbial metabolism, shaping nutritional and functional outcomes.

These factors—processing, maturity, and agronomic environment—determine the quantity and type of polyphenols in the diet, and influence their bioavailability. Furthermore, these same factors directly affect the production of colonic metabolites through microbial fermentation. Given these interconnected effects, the nutritional and functional potential of polyphenols must be assessed holistically. This holistic assessment requires

considering their presence in raw materials as well as their fate during food transformation, digestion, and microbial metabolism.

Table 3. Principal factors affecting polyphenol content and its subsequent biological implications.

Factor Influencing Polyphenol Content	Description	Biological Implication
Processing	Drying, thermal treatment, fermentation, and mechanical processing can degrade, tianstorm or release polyphenols from plant	Alters structure and bioactivity, affects colonic availability
Ripeness and harvest timing	Levels of anthocyanins, flavan-3-ols, and flavonols vary significantly with ripening, with optimum harvest being matrix-dependent	Modulates precursor availability for colonic bioconversion
Agricultural and environmental conditions	Organic practices; UV exposure, altitude, and water availability con modify, polyphenol biosynthesis via stress responses	Affects content and profile of phenctic compounds in crops

2.3. Polyphenol Structural Diversity and Biological Relevance

Polyphenols vary greatly in structure. Hydroxylation, glycosylation, and polymerization determine solubility, stability, metabolism, and bioactivity. Native forms often need microbial or enzymatic conversion into smaller, more absorbable metabolites to exert biological effects [26].

Stilbenes. Resveratrol (trans-3,5,4′-trihydroxystilbene) has potent antioxidant activity but low bioavailability. Microbial conversion to dihydroresveratrol and lunularin may enhance activity. Methylated forms like pterostilbene improve lipophilicity and absorption [27–29].

Lignans. Plant lignans such as secoisolariciresinol diglucoside from flaxseed depend on microbial deglycosylation and O-demethylation to produce enterodiol and enterolactone—lipophilic metabolites with estrogenic, antioxidant, and anti-inflammatory properties [30].

Tannins include hydrolyzable (ellagitannins) and condensed (proanthocyanidins) forms. These are large, highly hydroxylated molecules that reach the colon largely intact. There, microbial depolymerization yields catechins, phenolic acids, valerolactones, and urolithins—metabolites with potent systemic effects [26,31–38].

Overall, microbial metabolism converts structurally complex dietary polyphenols into low-molecular-weight polyphenol metabolites (LMWPMs) that mediate their health-promoting properties.

2.4. Microbial Transformation of Polyphenols

Polyphenols exhibit a diverse range of biological activities in vitro. However, their in vivo effects largely depend on microbial catabolism. Due to their large size, low solubility, and rapid conjugation (via glucuronidation, sulfation, and methylation), less than 10% of dietary polyphenols are absorbed in the small intestine. Most reach the colon [39]. In the colon, gut microbes convert polyphenols into LMWPMs with a molecular weight of less than 300 Da. These include phenylacetic acids, hydroxyphenylpropionic acids, γ-valerolactones, and urolithins [40,41]. These metabolites exhibit enhanced bioavailability, antioxidant, anti-inflammatory, neuroprotective, and anti-biofilm activities. Key microbial enzymes, such as β-glucosidases, esterases, reductases, decarboxylases, and dehydroxylases, facilitate hydrolysis, reduction, and ring cleavage. These processes produce metabolites that cross biological barriers such as the intestinal mucosa and the blood–brain

barrier [42–45]. Table 4 presents the microbial pathways and the primary enzymes involved in polyphenol metabolism.

Table 4. Microbial pathways and enzymes involved in polyphenol metabolism.

Polyphenol Class	Microbial Transformation Pathways	Key Enzymes	Representative Metabolites
Flavan-3-ols	Ring fission, dehydroxylation, and decarboxylation	Reductases, dehydroxylases, esterases	5-(3′,4′-Dihydroxyphenyl)-γ-valerolactone; Hydroxyphenylpropionic acids [46–49]
Ellagitannins	Hydrolysis, lactonization	Tannase, decarboxylases	Urolithins (A, B, C, D) [44,50]
Flavonols	Deglycosylation, dehydroxylation	β-Glucosidases, reductases	Phenylacetic acids, phenylpropionic acids [51–53]
Anthocyanins	Deglycosylation, ring cleavage	β-Glucosidases, esterases	Protocatechuic acid, gallic acid [21,53,54]
Stilbenes	Hydrogenation, dehydroxylation	Reductases, dehydroxylases	Dihydroresveratrol, lunularin [54]
Lignans	Demethylation, dehydroxylation, dehydrogenation	β-Glucosidases, dehydrogenases	Enterodiol, enterolactone [55,56].
Tannins (general hydrolysable)	Hydrolysis, microbial fermentation	Esterases, decarboxylases	Gallic acid, pyrogallol, catechol derivatives [57]

Specific taxa, including *Gordonibacter*, *Eggerthella*, *Clostridiales*, and *Slackia*, play a central role in these pathways, generating urolithins, valerolactones, and dihydroresveratrol [37,58–61]. Distinct classes of polyphenols, such as flavonoids, stilbenes, lignans, and phenolic acids, undergo degradation pathways regulated by specialized microbial enzymes and taxa. For example, ellagitannins are transformed into urolithins by *Gordonibacter urolithinfaciens* and *Ellagibacter isourolithinifaciens*, flavan-3-ols into valerolactones by *Clostridiales* and *Eggerthellaceae*, and resveratrol into dihydroresveratrol by *Slackia equolifaciens* [60]. Variations in gut microbial composition and enzyme activity result in distinct metabotypes, which influence an individual's ability to metabolize and respond to polyphenols. For instance, some individuals convert isoflavones to equol, while others do not. Comparable differences are observed for ellagitannins, resulting in urolithin metabotypes A, B, or 0, and for resveratrol, as either producers or non-producers of lunularin. Individuals who produce urolithin often demonstrate enhanced cellular energy production, whereas those who produce valerolactone may experience improved cognitive function and reduced inflammation. Thus, microbial breakdown is essential to the physiological effects of dietary polyphenols.

The relationship between dietary polyphenols and the gut microbiota is increasingly viewed as a symbiotic dialogue, rather than a unidirectional interaction. In this dynamic crosstalk, polyphenols are both sculptors and clay—they shape the microbial community while simultaneously being transformed by it. The result is the production of minor, bioactive compounds—postbiotic metabolites—that can exert systemic effects on the host.

This bidirectional relationship can be deconstructed into several interconnected mechanisms: microbial biotransformation, compositional modulation, functional gene enrichment, and feedback amplification. Table 5 shows the function exhibited by specific metabolites produced by the principal microbial genera. All such processes can support the development of personalized nutrition strategies. Further research into these molecules may also inform dietary interventions for individuals with inflammation, infections, or neurological disorders.

Table 5. The main classes of microbial metabolites, the dominant microbial taxa involved, and their functional health effects.

Microbial Metabolites	Main Microbial Genera	Functional Outcomes
Urolithins A, B, C, D	*Gordonibacter*, *Ellagibacter*, *Akkermansia*	Anti-inflammatory, anti-biofilm, mitochondrial biogenesis [37,62–64]
γ-Valerolactones, hydroxyvaleric acids	*Clostridium*, *Eubacterium*, *Blautia*, *Flavonifractor plautii*, *Eggerthella*, *Lactobacillus*	BBB modulation, QS inhibition, redox regulation [33,65–67]
Protocatechuic acid, hippuric acid, phloroglucinol	*Bifidobacterium*, *Lactobacillus*, *Bacteroides*	Antioxidant, barrier protection, microbial modulation [68–70]
Dihydroresveratrol, lunularin	*Eggerthella lenta*, *Slackia equolifaciens*, *Adlercreutzia*	Anti-amyloidogenic, estrogenic modulation, neuroprotective, antifungal [43,54]
Hydroxyphenylpropionic acids, benzoic acids	*Faecalibacterium*, *Roseburia*, *Anaerostipes*	SCFA co-production, TLR modulation, colonocyte health [71–74]
Equol, O-desmethylangolensin	*Slackia*, *Adlercreutzia*, *Eggerthella*	Estrogen receptor modulation, antioxidant, neuroprotection [75–77]
Enterodiol, enterolactone	*Bacteroides*, *Ruminococcus*, *Clostridium*, *Eggerthella*	Antiproliferative, estrogenic/anti-estrogenic, cardioprotective, antioxidant, cardioprotective [71,78–80]
3,4-dihydroxyphenylacetic acid, phenylacetic acid	*Eubacterium*, *Lactobacillus*, *Bacteroides*	Anti-inflammatory, immune modulation, antioxidant, intestinal protection [52,81–83]
8-prenyl-naringenin	*Eubacterium limosum*	Estrogen modulation, antioxidant activity [84,85]
Tetrahydrocurcumin, dihydrocaffeic acid	*Escherichia coli*, *Blautia*, *Clostridium*	Anti-inflammatory, immune modulation, antioxidant [59,86]
Caffeic acid, ferulic acid	*Bifidobacterium*, *Lactobacillus*, *Eubacterium*	Glycemic modulation, antioxidant, liver protection [87–89]
3-(4-hydroxyphenyl) propionic acid	*Clostridium*, *Eubacterium*, *Bacteroides*	Anti-inflammatory, lipid modulation, cardiovascular protection [44,86]
Gallic acid, ellagic acid	*Lactobacillus*, *Bifidobacterium*, *Streptococcus*	Antimicrobial, immune modulation, gut protection [45,90]
Phenylpropionic acid, phenylacetic acid	*Bacteroides*, *Clostridium*, *Eubacterium*	Antioxidant, microbiota modulation, cardiovascular protection [52,91,92]
3,4-dihydroxyphenylacetic acid, protocatechuic acid	*Bacteroides*, *Clostridium*, *Eubacterium*	Anti-inflammatory, immune modulation, intestinal protection [21,48,83,90]

2.5. Biofunctional Properties of LMWPMs

A growing body of research highlights the biological relevance and pleiotropic activity of LMWPMs. These compounds, which are products of gut microbial metabolism of dietary polyphenols, are emerging as crucial players in managing human health challenges, particularly cardiovascular disease and neurodegenerative disorders. Despite their structural simplicity, LMWPMs exhibit remarkable bio-efficacy across various physiological systems. They often surpass their parent polyphenols in potency, specificity, and systemic availability.

- **Quorum Sensing Inhibition and Anti-Biofilm Activity**

Multiple LMWPMs interfere with quorum sensing (QS), the bacterial communication system that regulates virulence and biofilm development. This includes the disruption of foodborne pathogens. In the complex gut environment, these interactions become even more significant. By disrupting QS mechanisms, LMWPMs can influence not just isolated pathogens, but also the larger microbial consortia in the gut. This may alter microbial dynamics to favor gut health. For example, urolithin A inhibits the *agr* and *sar*A systems in *Staphylococcus aureus.* This attenuates biofilm maturation without affecting planktonic growth. Similarly, 3,4-dihydroxyphenylacetic acid, a flavonoid catabolite, disrupts AI-2–mediated signaling in *E. coli.* This impairs adhesion and EPS synthesis. These activities

often occur at sub-inhibitory concentrations. As a result, selective pressure and the risk of antimicrobial resistance are reduced [93,94].

– **Neuroactive Potential and Blood–Brain Barrier Interaction**

Certain LMWPMs can cross the blood-brain barrier (BBB) and interact with neuronal and glial targets, highlighting their potential role in the gut-brain axis. Recognizing the bidirectional signaling between gut microbes and the brain helps us understand how these compounds fit into neural pathways influenced by the microbiota [55–97]. Furthermore, they can act either directly or by modulating systemic inflammation. For example, dihydroresveratrol exhibits neuroprotective effects by decreasing microglial activation and reducing the expression of TNF-α and IL-6 in the hippocampus. Additionally, urolithin A promotes mitochondrial biogenesis and autophagy (mitophagy) in neuronal models, resulting in enhanced synaptic function and improved memory performance in aging mice. Similarly, some valerolactones modulate monoaminergic signaling, including dopamine and serotonin, suggesting a role in mood and cognitive regulation. Finally, due to their small size, increased lipophilicity, and efficient transporter utilization, LMWPMs cross the blood-brain barrier more readily than their parent polyphenols [97,98].

– **Enhancement of Gut Barrier Function**

Several LMWPMs support intestinal epithelial integrity, which is essential for immune homeostasis and preventing systemic inflammation. Urolithins and phenolic acids upregulate tight junction proteins, including occludin, claudin-1, and ZO-1, in Caco-2 and organoid models. These effects correlate with reduced paracellular permeability and lower endotoxemia in LPS-induced inflammation models. These properties position LMWPMs as potential therapeutic agents for conditions such as increased intestinal permeability, inflammatory bowel diseases (including Crohn's disease and ulcerative colitis), metabolic syndrome, and neurological disorders [98,99].

– **Epigenetic Modulation and Gene Regulation**

An emerging dimension of LMWPM activity involves epigenetic mechanisms, including inhibition of histone deacetylases (HDACs), which promotes chromatin relaxation and gene transcription, contributing to antioxidant and anti-inflammatory responses. MicroRNA (miRNA) modulation similarly affects apoptosis, cytokine production, and neural plasticity. For example, protocatechuic acid downregulates miR-155 and upregulates miR-146a in macrophages, balancing pro- and anti-inflammatory cytokines [100]. Urolithin B inhibits HDAC1 and HDAC3 in cancer and neurodegeneration models, reactivating neuroprotective genes. Thus, dietary polyphenols and their microbial conversion into LMWPMs are key drivers of these epigenetic shifts, underscoring the synergy between microbiome modulation and gene expression. These activities open new avenues for nutritional epigenetics and postbiotic-based gene modulation strategies [97,98].

2.6. Relationship Between Dietary Polyphenols and the Gut Microbiota

The relationship between dietary polyphenols and the gut microbiota is now viewed as a symbiotic dialogue. Polyphenols shape microbial community composition, while the microbiota converts them into smaller, bioactive postbiotic metabolites with systemic effects. This bidirectional exchange involves microbial metabolism of polyphenols, polyphenol-driven modulation of microbiota structure, gene activation, and the cumulative outcomes of these interconnected processes. Table 6 and Figure 2 provide a summary of these processes.

Table 6. Summary of key mechanisms underlying polyphenol–microbiota interactions, highlighting microbial transformation, selective modulation of gut taxa, functional gene induction, feedback loops, and downstream immunometabolic effects.

Aspect	Mechanism	Examples
Microbial metabolism of polyphenols	Microbial enzymes degrade polyphenols into more minor, bioactive metabolites	β-glucosidases, esterases, reductases; production of urolithins, valerolactones, hydroxyphenylacetic acids. [46,48]
Microbiota modulation by polyphenols	Selective growth promotion of beneficial microbes and suppression of pathogens	↑ *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*; ↓ *Clostridium* spp., Enterobacteriaceae [52,60,61,101–104]
Functional gene enrichment	Polyphenol intake increases the abundance of microbial genes involved in polyphenol catabolism.	Tannase, phenolic acid decarboxylase genes [45,104]
Feedback amplification of biotransformation	Polyphenol-induced taxa enhance further degradation of polyphenols into more minor metabolites.	Increased production of urolithins and hydroxycinnamic acid derivatives with repeated intake [21,46]

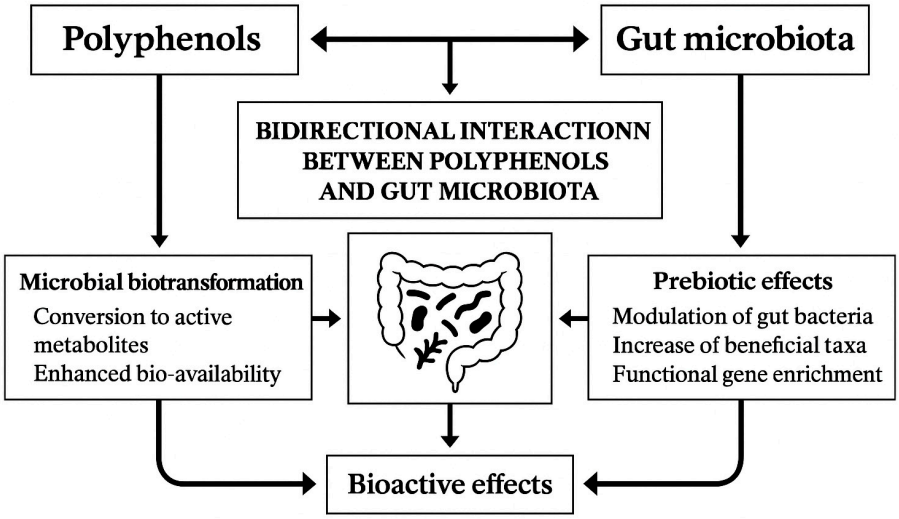

Figure 2. Scenario of the bidirectional interaction between polyphenols and gut microbiota.

Extensive in vitro and in vivo research shows that polyphenol-rich foods—such as berries, pomegranate, tea, cocoa, and red wine—promote the growth of beneficial gut microorganisms, including *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, and *Bifidobacterium* spp. Sustained intake of these foods selectively enriches health-promoting taxa. For example, *A. muciniphila*, enhanced by ellagitannin- and flavonol-rich diets, supports gut barrier integrity and reduces metabolic inflammation, while *F. prausnitzii* is stimulated by catechins and chlorogenic acids. *Bifidobacterium* spp., which initiate flavonoid deglycosylation, also benefit from the prebiotic effects of polyphenols and their metabolites, helping maintain eubiosis [46,104]. Anthocyanin intake similarly improves microbiota composition and diversity, promoting the growth of *Bifidobacterium*, *Faecalibacterium*, and *Lactobacillus* [105,106]. Grape polyphenols have been shown to increase *A. muciniphila* abundance and modulate gut barrier parameters in mice [107]. Polyphenol-rich diets also reduce pathobionts such as *Clostridium*, *Fusobacterium nucleatum*, and *Enterobacteriaceae*, contributing to a healthier microbial balance [108–111].

Polyphenols and their microbial catabolites exert selective antimicrobial activity, suppressing opportunistic and pathogenic taxa at sub-inhibitory concentrations while sparing beneficial commensals [112–115]. Flavanol- and phenolic acid-rich foods significantly reduce *C. perfringens* and *Enterobacteriaceae*, highlighting their potential to mitigate dysbio-

sis [45,62]. Microbial metabolites of polyphenols also exhibit selective antimicrobial effects; for instance, the consumption of green tea lowers the levels of faecal *Enterobacteriaceae* and *Clostridium* spp., indicating synergistic prebiotic and antimicrobial actions [116]. Overall, these findings suggest that polyphenols act both as microbial substrates and as modulators of microbial ecology, enhancing their own biotransformation and systemic benefits.

2.7. Polyphenol Bioavailability and Microbiota-Driven Biotransformation

Microbial catabolites—produced when gut bacteria break down polyphenols—often exhibit higher absorption, better membrane permeability, and greater biological activity than their parent compounds, substantially contributing to the health benefits of polyphenol-rich diets. The generation of these low-molecular-weight bioactive metabolites depends on both host factors and the gut microbiota.

Among these factors, the composition of the microbiota plays a key role, serving as a primary determinant that links host and dietary influences on bioconversion outcomes. Individual differences in gut microbiota strongly affect polyphenol metabolism. Specific taxa, such as *Gordonibacter*, *Eggerthella*, *Slackia*, and *Adlercreutzia*, catalyze key transformations, including the formation of urolithin and equol, which define distinct metabotypes and bioactive profiles.

Furthermore, in addition to microbial factors, dietary and structural elements also influence the bioconversion process, underscoring the multifactorial nature of polyphenol metabolism. Food matrix (the nutrient and non-nutrient components of food) and polyphenol structure determine how easily polyphenols are accessible to the body and exposed to microbes. Fibers favour colonic (large intestine) metabolism, fats promote early absorption of polyphenols that dissolve in fats (lipophilic compounds), and protein binding lowers availability [108–111].

In parallel, host physiology further modulates these metabolic processes, integrating internal environmental conditions into the overall metabolic landscape. Colonic pH, transit time, and oxygen influence microbial activity. Longer transit and mildly acidic, anaerobic conditions enhance conversion. High levels of bile acids from diets rich in fat reduce microbial diversity.

Finally, external influences and genetic background are additional determinants that interact dynamically with microbial and host-related factors. Antibiotics suppress key metabolizers (microbes responsible for breaking down polyphenols), while probiotics (beneficial microbes) and prebiotics (food components that support beneficial microbes) enhance the production of short-chain fatty acids (SCFA) and other beneficial metabolites. Age, sex, genetics, and disease states (such as inflammatory bowel disease (IBD) and obesity) influence microbial composition and transformation capacity.

3. Anti-Biofilm Activity of Polyphenol-Derived Metabolites

3.1. Antimicrobial Resistance and Foodborne Pathogens

Antimicrobial resistance (AMR) is a major global health threat [112–117]. Infections caused by antibiotic-resistant pathogens result in greater disease severity and frequent treatment failures in both humans and animals [118,119]. The misuse and overuse of antibiotics in agriculture and the food industry have accelerated the emergence of resistant strains [120], with up to 80% of antibiotics in some countries—such as the United States—used in animal farming [121]. Globally, antibiotic-resistant infections cause an estimated 1.2 million deaths each year [122]. Foodborne pathogens, such as *Campylobacter*, *Salmonella*, *E. coli* O157, *Listeria monocytogenes*, *S. aureus*, and *Clostridium*, infect approximately one in six people worldwide each year [123], often without altering the appearance or sensory qualities of food, which complicates safety assessments [124]. Foodborne pathogens can

also cause spoilage and toxin production. These agents contribute significantly to morbidity and mortality. The increased consumption of ready-to-eat foods further exacerbates food safety challenges. Understanding the pathogenic mechanisms of these microorganisms supports advances in epidemiology and detection methods. It also enhances diagnostics and facilitates the development of interventions, including vaccines, pharmaceuticals, and bioactive molecules—such as polyphenols and their metabolites—for the prevention and control of diseases.

3.2. Pathogenic Biofilms

Biofilms are structured microbial communities embedded in a self-produced extracellular polymeric substance (EPS) matrix that adheres to various surfaces [125]. These consortia demonstrate significant resistance to antimicrobial agents, host immune defenses, and environmental stressors, which present major challenges in both clinical and food safety contexts. Bacteria within biofilms can survive antimicrobial concentrations up to 1000 times higher than those required to inhibit planktonic cells, thereby contributing to persistent infections [126]. Polyphenols and their derivatives exhibit broad-spectrum antimicrobial activity [127–129]. Their microbial metabolites exert multifaceted, non-lethal effects by targeting signaling pathways and structural elements essential for biofilm development, resulting in the destabilization of biofilms, increased dispersal, and heightened susceptibility to antimicrobials. Polyphenols also inhibit quorum sensing, disrupt cellular membranes, suppress enzymatic activity, induce reactive oxygen species (ROS), modulate immune responses, and block viral entry and replication. These mechanisms collectively enable polyphenols to eliminate microbial species. For instance, enzyme inhibition impairs metabolism, membrane disruption leads to cell death, ROS generation causes oxidative damage, quorum-sensing interference affects gene regulation and biofilm formation, and immune modulation strengthens host defense. The precise mechanisms depend on the microorganism, metabolite structure, and environmental conditions. Notably, membrane disruption is a principal antibacterial action of polyphenols [128,130]; interaction with lipid bilayers alters membrane permeability, damages membrane proteins, generates ROS, and ultimately results in cell lysis. Consequently, polyphenols are regarded as effective antifungal, antiviral, and antibacterial agents, and remain central to anti-infective research [127,131,132]. Furthermore, microbial-derived metabolites, such as urolithins, valerolactones, phenylpropionic acids, and dihydrocaffeic acid, frequently demonstrate greater anti-biofilm activity than their parent compounds [129,133].

These metabolites are produced through gut microbial transformation of dietary polyphenols. They frequently demonstrate enhanced bioavailability, stability, and tissue penetration. At sub-inhibitory concentrations, these compounds impair biofilm formation, maturation, or maintenance. They do this without compromising bacterial viability. Consequently, they reduce selective pressure for resistance and help preserve commensal microbial balance.

Microbial-derived polyphenol metabolites have broad-spectrum anti-biofilm activity. They target both Gram-positive and Gram-negative bacteria, as well as fungi. These metabolites interfere with quorum sensing and inhibit cellular adhesion. They also disrupt the extracellular polymeric substance (EPS) matrix and suppress expression of virulence genes. These mechanisms are especially relevant in the context of increasing antimicrobial resistance [126]. Microbial degradation of tea catechins produces several metabolites. These include 3-O-methyl gallic acid, gallic acid, caffeic acid, 4-hydroxyphenylpropionic acid, phenylpropionic acid, and 4-hydroxyphenylacetic acid. All demonstrate antibacterial properties [87]. Urolithin A also shows significant antibacterial activity. It inhibits AHL-mediated quorum sensing, biofilm maturation, and bacterial motility [127,134,135].

3.3. Mechanisms of Action of Polyphenol-Derived Metabolites on Foodborne Biofilms

Polyphenols and their derivatives disrupt microbial membranes, compromising integrity or inducing cell death [136,137]. By inhibiting fatty acid biosynthesis through targeting FabG and FabI, EGCG and related compounds exert their effects. In contrast, galloyl groups enhance interactions with lipid bilayers, while catechins penetrate the hydrophobic core of phospholipid membranes, altering their structure [138,139]. Wang et al. [140] demonstrated that antibacterial potency increases with alkyl chain length and that EGCG causes nanoscale membrane damage in *E. coli* and *S. aureus*. Further studies linked *S. aureus* cell wall degradation to EGCG binding to peptidoglycan, while *E. coli* damage is associated with oxidative stress [141]. Together, these findings demonstrate distinct mechanisms against Gram-positive and Gram-negative bacteria [142].

Polyphenols also inhibit the aggregation of amyloid-like proteins, a key structural component of biofilms. Compounds such as quercetin, myricetin, EGCG, and PGG prevent amyloid fibrillation by stabilizing early oligomers, redirecting aggregation pathways, and weakening matrix integrity, thereby increasing susceptibility to antibiotics without affecting bacterial viability [143,144].

Polyphenol-derived metabolites physically interfere with biofilm matrix formation by altering surface properties. By increasing electrostatic repulsion, hydrophilicity, and steric hindrance, they reduce bacterial adhesion and prevent the early establishment of biofilms [145]. Their negatively charged groups enhance surface charge, forming thin molecular layers (~10–20 nm) that act as barriers to attachment. Increased hydrophilicity further decreases bacterial affinity, reducing colonization by *S. aureus* and *E. coli*. These electrostatic and steric effects effectively inhibit biofilm formation in vitro and in vivo, including cell culture and wound models [146–151].

3.4. Quorum Sensing Modulation

Polyphenol-derived metabolites interfere with bacterial communication, known as quorum sensing, through several mechanisms. These metabolites degrade chemical signals, including acyl-homoserine lactones (AHLs) in Gram-negative bacteria and autoinducing peptides (AIPs) in Gram-positive bacteria, thereby reducing their half-lives from hours to minutes and preventing the activation of genes associated with biofilm formation. Additionally, polyphenol metabolites compete for signal-binding sites, block receptor activation, and inhibit the expression of quorum-sensing–regulated genes, thereby decreasing the production of virulence factors and biofilm formation. Compounds such as tea polyphenols and paeonol can also enhance antibiotic efficacy; for instance, catechins reduce the minimum inhibitory concentration (MIC) of oxacillin against *S. aureus*, demonstrating synergistic therapeutic potential. Disruption of these signalling pathways diminishes bacterial motility, virulence, and biofilm-forming ability, increasing susceptibility to host immune defences and antimicrobial agents. Furthermore, polyphenol metabolites may influence communication between bacteria and host cells, thereby affecting biofilm development and modulating immune responses.

3.5. Polyphenol-Derived Metabolites Most Effectively Target Which Food-Borne Pathogens?

Polyphenol-derived metabolites target pathogens, including *E. coli* O157, *S. aureus*, *Salmonella Typhimurium*, *Bacillus cereus*, *L. monocytogenes*, *Enterococcus faecalis*, and *Enterobacter sakazakii*. Polyphenols, such as baicalein, myricetin, hesperetin, and quercetin, can act as bacteriostatic or bactericidal agents, depending on the strain and structure.

***E. coli* O157**: polyphenol-derived metabolites, such as phloretin from apples, downregulate the curli genes (*csgA* and *csgB*), thereby reducing bacterial attachment and weakening the biofilm structure [152].

S. aureus (including MRSA): Tannic acid increases IsaA protein levels, inhibiting biofilm maturation. Hydroxyl groups in flavonoid metabolites disrupt quorum sensing by binding to DNA and proteins, reducing the expression of virulence factors. These metabolites also enhance the effectiveness of antibiotics, such as oxacillin, by weakening biofilm defences, including the *agr* system [94].

Salmonella: polyphenol metabolites inhibit biofilm formation by disrupting the synthesis and motility of extracellular substances [153,154]. Biotin-tagged derivatives target biofilm stability and enhance the efficacy of ciprofloxacin. Some metabolites may downregulate T3SS regulators, limiting biofilm and invasion; further studies are needed. EGCG blocks quorum sensing and the type III secretion system (T3SS), affecting motility and biofilm development. More validation is required for hydroxyphenylvaleric acids and valerolactones [155–158].

Enterobacter sakazakii: various polyphenolic compounds reduce biofilm formation and virulence gene expression. Coenzyme Q10 downregulates biofilm and virulence genes, reducing adhesion and motility. Chlorogenic acid disrupts membrane potential, ATP production, pH balance, and cellular morphology [159–161].

Vibrio parahaemolyticus: this microorganism shows resistance, prompting the study of plant-derived compounds. Flavonoids disrupt bacterial membranes, while albofungin damages biofilms by affecting cell structures [162–164].

Enterococcus faecalis: terpenoid and flavonoid metabolites suppress virulence genes (esp, gelE), reduce biofilm adhesion, and inhibit the release of extracellular DNA needed for stability. Curcuminoids reduce biofilm biomass by more than 70% at sub-MIC doses [165].

B. cereus: Polyphenol-derived acids like gallic acid disrupt its membrane potential and inhibit spore and biofilm formation.

L. monocytogenes: This pathogen contains key virulence gene clusters, including LIPI-1 and the InlA/InlB operon, essential for invasion and survival [166]. Polyphenol-derived metabolites negatively modulate these genes by inhibiting activation of virulence factors, altering surface proteins, inducing oxidative stress, and affecting quorum sensing, reducing adhesion, invasion, and biofilm formation [166–169].

3.6. Anti-Biofilm Activity of Polyphenol-Derived Microbial Metabolites

Microbial metabolites of dietary polyphenols inhibit biofilm formation in Gram-positive and Gram-negative foodborne bacteria. Their mechanisms include quorum-sensing interference, prevention of adhesion, EPS disruption, and suppression of virulence genes. These features are especially relevant given the rising prevalence of antimicrobial resistance and the need for non-bactericidal strategies [170–172]. For example, ellagitannins create hydrolyzed metabolites that inhibit AHL synthases, demonstrating anti-QS effects [173].

Urolithins A and B can impair the motility and adhesion of *L. monocytogenes* on food-processing surfaces, potentially reducing biofilm formation [174]. They also inhibit quorum-sensing systems in pathogens such as *Yersinia enterocolitica*, *Shigella dysenteriae*, *Vibrio cholerae*, *Campylobacter* spp., and MRSA by lowering AHL levels and blocking motility and maturation pathways [50,134,135,143]. Urolithin A additionally reduces *C. difficile* toxin expression without killing cells, indicating a gene-level effect. Several urolithins and derivatives show distinct antibacterial activities. Valerolactone metabolites, such as 5-(3′,4′-dihydroxyphenyl)-γ-valerolactone and its conjugates, show strong anti-adhesive effects against uropathogenic *E. coli* (UPEC), with sulfated derivatives most active at 100 μM [49]. Other microbial metabolites of tea catechins, including 3-O-methyl gallic acid, gallic acid, caffeic acid, phenylpropionic acid, and 4-hydroxyphenylacetic acid, also have antibacterial properties [87]. Compounds like 3,4-dihydroxyphenylacetic acid inhibit UPEC adhesion in a concentration-dependent way [175], and 3,4-dihydroxyphenylpropionic acid may modulate *E. coli* growth dynamics [81].

Phenyl-lactic acid (PLA) derivatives inhibit biofilms by disrupting motility, chemotaxis, quorum sensing, and polysaccharide production, as well as reducing respiratory chain activity. They can also compromise membrane integrity in *S. aureus* and *S. enteritidis*, leading to ATP leakage [176]. Hydroxyphenylacetic acid and 3,4-DHPA sensitize *Salmonella* to novobiocin [177], and related metabolites can reduce *E. coli* resistance to β-lactams and aminoglycosides [178].

3.7. Synergy with Antimicrobials

The increasing prevalence of biofilm-associated infections and antimicrobial resistance (AMR) has sparked significant interest in combination therapies that enhance the effectiveness of conventional antibiotics. Polyphenol-rich plant extracts and their microbial metabolites have shown synergistic or additive effects with various antimicrobial agents, especially against biofilm-forming pathogens. These combinations can reduce antibiotic dosages, restore activity against resistant strains, and potentially shorten treatment durations or decrease side effects [179,180].

Examples of synergistic combinations: Polyphenols derived from green propolis, *Tabebuia avellanedae* bark, and *Olea europaea* leaf extracts demonstrate synergistic activity with macrolide antibiotics, including azithromycin and clarithromycin, against *S. aureus*. This synergy results in reduced minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) values, as well as enhanced bactericidal effects in time-kill assays [179–181]. In extension to these findings in Gram-positive bacteria, combinations such as colistin with the adjuvant PFK-158 have also been shown to synergistically inhibit biofilm formation in Gram-negative bacteria, indicating that comparable polyphenol-based strategies may be effective in this context as well [182]. Therefore, these results collectively support the application of polyphenol-rich extracts and their metabolites, alongside antibiotics, to manage chronic and biofilm-associated infections, resensitize resistant strains, and reduce selective pressure [183]. Furthermore, as polyphenols primarily target bacterial communication and physiology rather than viability, they may also contribute to the preservation of commensal microbiota. Tables 7 and 8 and Figures 3 and 4 summarize the anti-quorum-sensing and antibiofilm actions of polyphenol-derived metabolites.

Table 7. Mechanistic anti-biofilm actions of polyphenol-derived molecules, Abbreviations: QS, quorum sensing; EPS, extracellular polymeric substances; AHL/AIP, acyl-homoserine lactone/autoinducing peptide; PVLs, phenyl-γ-valerolactones; DOPAC, 3,4-dihydroxyphenylacetic acid; T3SS, type III secretion system.

Class	Mechanism	Anti-Biofilm Outcomes
Urolithins (A/B)	QS interference; antivirulence at sub-MIC	↓ AHLs, ↓ motility, ↓ biofilm maturation; reduced toxin expression (e.g., *C. difficile*) [134,184,185]
PVLs & hydroxyphenylvaleric acids	Anti-adhesive; QS attenuation	↓ adhesion to bladder cells; ↓ initial attachment; putative repression of virulence in enterics [42]
DOPAC, 3,4-DHPPA, 3-HPA	Anti-adhesive; antibiotic sensitization	↓ adhesion (UPEC, *Salmonella*); ↑ susceptibility to novobiocin; virulence attenuation [81,177]
Polyphenol metabolites (general)	Membrane & macromolecule disruption	Membrane depolarization; ROS-mediated damage; cell lysis (strain-dependent) [137–140,142]
EGCG and galloylated flavonoids	Anti-amyloid (biofilm matrix); membrane effects	Off-pathway oligomers; weakened matrix; ↓ biomass; ↑ antibiotic susceptibility [104,144]
Surface-active metabolites/coatings	Physical interference with adhesion/EPS	↑ electrostatic repulsion; ↑ hydrophilicity; ↓ initial attachment [145]
Combinations (polyphenols-derived metabolites + antibiotics)	Synergy/sensitization	↓ MIC/MBC; restored activity vs. resistant biofilms; ↓ selective pressure [170,179,180]

Table 8. Summary of the foodborne pathogen-focused evidence and polyphenols-derived metabolites actions, and specific readouts (adhesion, QS, EPS, virulence, antifungal morphogenesis). Where mechanisms are inferred from close analogues (e.g., catechin → valerolactone), this is noted in text.

Pathogen	Polyphenols	Readouts
Uropathogenic *E. coli* (UPEC), *E. coli* O157	PVLs; DOPAC; phenolic acids	↓ adherence to T24 cells; dose-dependent anti-adhesion [49,94,152]
S. aureus/MRSA	EGCG, tannic acid; phenolics	↓ biofilm maturation; ↑ IsaA; ↑ antibiotic efficacy [94,144].
S. enterica	Catechin-derived metabolites (PVLs, HPVAs) (inference); EGCG	↓ biofilm; ↓ virulence; synergy with ciprofloxacin (in vivo) [153,155]
C. sakazakii	Coenzyme Q0; chlorogenic acid	↓ adhesion/motility; biofilm disruption [161]
L. monocytogenes	Quercetin; EGCG; general phenolics	↓ adhesion/invasion; ↓ hemolysis; ↓ biofilm [167–169]
General AMR context	polyphenols-derived metabolites + antibiotics	Enhanced efficacy vs. biofilms; ↓ resistance pressure [179,180,183]

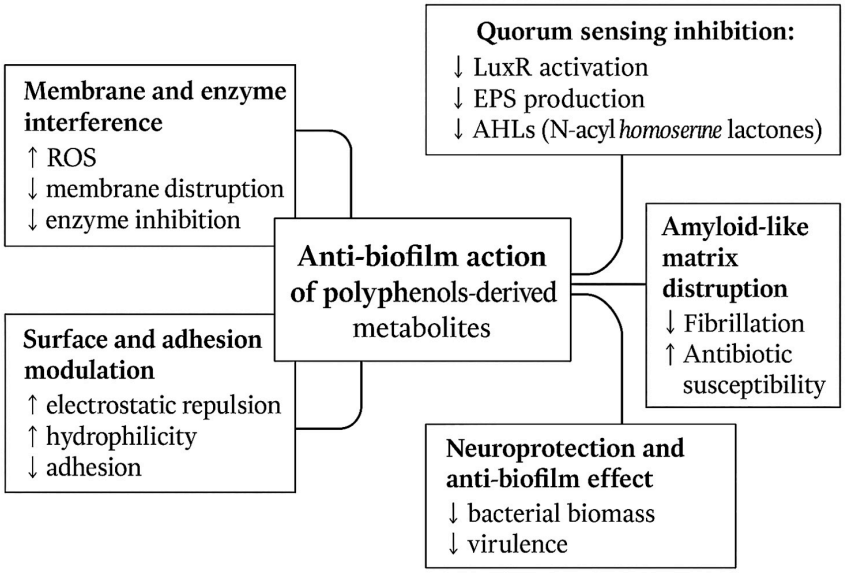

Figure 3. Scheme of convergent mechanisms used by polyphenol-derived metabolites against pathogenic bacteria: Quorum sensing inhibition (blocking bacterial communication); Amyloid-like matrix inhibition (interfering with Bap/FapC and increasing antibiotic penetration); Surface and adhesion modulation (enhancing electrostatic repulsion and hydrophilicity, reducing adhesion); Synergy and sensitization (lowering biomass and virulence, increasing antibiotic susceptibility). Captions: AHLs = N-acyl homoserine lactones; LuxR = quorum-sensing transcriptional regulators; EPS = Extracellular Polymeric Substances; ROS = Reactive Oxygen Species.

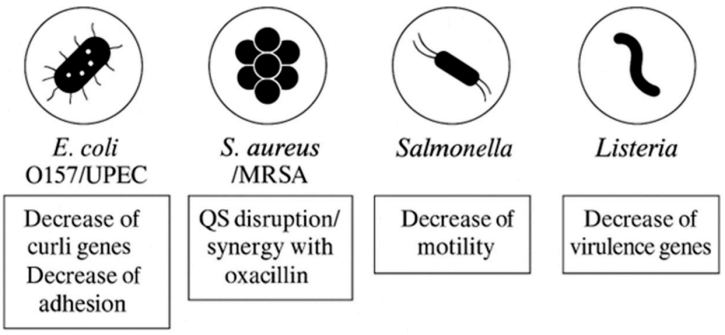

Figure 4. Overview of some representative foodborne pathogens (*E. coli* O157/UPEC, Methicillin-resistant *S. aureus* (MRSA), *Salmonella*, *Listeria*) with dominant antibiofilm actions (anti-adhesive, anti-QS, anti-matrix, membrane disruption, antivirulence) by polyphenol-derived metabolites.

4. Neuroprotective Properties of Polyphenol-Derived Metabolites and the Gut–Brain Axis

Metabolites produced from dietary polyphenols by gut microbiota act on both pathogenic bacteria and the central nervous system. These bioavailable compounds have antimicrobial and anti-biofilm properties, including effectiveness against foodborne pathogens that cross the intestinal and blood–brain barriers. They also modulate neuroinflammation and offer antioxidant and neuroprotective benefits. Together, these actions make polyphenol-derived metabolites important mediators connecting gut health, infection control, and neurodegenerative processes.

4.1. The Gut–Brain Axis and Foodborne Pathogens

The gut–brain axis (GBA) is a bidirectional communication network that links the gut and brain through various pathways, including immune, hormonal, neural, and microbial pathways. This system regulates digestion, immunity, and behavior, but can be disrupted by foodborne pathogens, which trigger gastrointestinal disease and neuroinflammation. Pathogens induce gut immune responses, releasing cytokines that affect mood, cognition, and stress responses [186]. Chronic inflammation from persistent infections can contribute to disorders such as IBS, where altered gut activity influences brain function. By disturbing microbial diversity, pathogens create dysbiosis that transmits abnormal signals to the brain, potentially leading to anxiety, depression, or cognitive changes. Infections such as *Salmonella* or *Clostridium difficile* can also impair neurotransmitter production, including serotonin, leading to nausea, anxiety, and long-term behavioral effects [187–189]. Increased gut sensitivity resulting from infection generates pain signals transmitted to the brain, contributing to the development of functional gastrointestinal disorders [190].

The GBA affects immunity and drug metabolism by altering how cells respond to stress caused by pathogen-driven inflammation and microbial imbalances. These changes can reduce the effectiveness of chemotherapy. For example, *Salmonella*'s virulence factors can alter host chromatin, disrupt DNA methylation and histone modification, and activate NF-κB and STAT3, all of which contribute to cancer progression and treatment resistance [191]. Non-coding RNAs, such as miR-21, miR-155, and lncRNAs, regulate cell growth, death, and drug removal, suggesting potential treatments, including probiotics or drugs targeting epigenetic enzymes (HDACs, DNMTs) [192].

Foodborne infections—bacterial, parasitic, or viral—pose a significant global health threat and can elicit neuroinflammatory responses, despite primarily affecting the gut [193]. Key mechanisms include GBA-mediated reshaping of the microbiota, which generates systemic inflammation affecting organs such as neuronal tissues [194,195]. Pathogens can compromise intestinal integrity, known as "leaky gut," allowing microbes and inflammatory mediators to access the brain [196]. Bacterial metabolites and toxins may accumulate in brain tissue, damage the blood–brain barrier (BBB), and activate cytokine-driven neuroinflammation [197]. These processes link foodborne pathogens to chronic neurological conditions, including brain abscesses, meningoencephalitis, Alzheimer's disease, Parkinson's disease, and rhombencephalitis, partly through the effects of neurotoxins and mycotoxins that disrupt BBB integrity [198,199].

4.2. Potential Mechanism of Pathogen-Associated Neurotoxicity

Many human diseases compromise brain tissue, and bacterial infections may cause substantial morbidity and mortality of the central nervous system (CNS), resulting in recurrent neurological disorders even in the presence of antibiotic therapy [200]. These outcomes occur in disorders transmitted via various routes, including gastrointestinal

infection. For instance, toxins secreted by foodborne pathogens such as *C. botulinum* can induce encephalopathy [201].

4.3. Foodborne Pathogens and Their Neurological Impact

E. coli and neuroinflammation. Certain strains of *E. coli* (particularly enterohemorrhagic EHEC) produce Shiga toxin, which can penetrate the intestinal epithelium and enter the bloodstream [202]. Once within the circulation, Shiga toxins can traverse the BBB, triggering inflammation and neurodegeneration [186,203]. Pathogen-induced inflammation activates microglia—the immune cells of the nervous system—resulting in chronic oxidative stress and neuronal injury [204].

Salmonella enterica and brain inflammation. Although *Salmonella* infections typically affect the intestinal tract, they can disseminate systemically, causing meningitis, particularly in individuals with compromised immune systems. Bacterial lipopolysaccharides (LPS) activate Toll-like receptors (TLRs) in the nervous system [205], promoting the release of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 [206]. This inflammatory cascade can contribute to both cognitive decline and neurodegenerative diseases.

L. monocytogenes and meningitis. One of the most important foodborne pathogens affecting the CNS is *L. monocytogenes*, which causes listeriosis. This bacterium can penetrate the intestinal barrier, enter the bloodstream, and cross the BBB to induce encephalitis and meningitis. The potent immune-mediated response elicited by *L. monocytogenes*, involving microglial activation and increased cytokine production, can lead to chronic neuroinflammation and neuronal degeneration [207].

C. botulinum and neurotoxicity. Botulinum neurotoxin (BoNT), produced by *C. botulinum*, is among the most potent neurotoxins known. Although BoNT is primarily associated with muscular paralysis, emerging evidence suggests it may also interfere with neuronal communication pathways. In the context of chronic neurodegenerative conditions, even low-dose exposure to *C. botulinum* toxins can provoke mild neuroinflammatory effects [208].

4.4. Neurotoxic Effects of Foodborne Toxins

The gut–brain axis plays a crucial role in regulating neuroinflammation [209]. Neurotoxins and metabolites produced by foodborne microbes can compromise the BBB integrity and activate glial cells within the cerebral cortex, triggering neuroinflammation and disrupting neurotransmission [210]. The severity of these neurological effects is influenced by both toxin concentration and the host's physiological response [186]. For instance, *L. monocytogenes* secretes Listeriolysin O (LLO), which traverses the BBB via circulating cells and interacts with receptors such as InlA, InlB, and Vip, resulting in conditions including meningitis, encephalitis, brain abscesses, and rhombencephalitis [199,211]. Similarly, *C. botulinum* neurotoxin readily crosses the BBB and disrupts the gut–brain axis, leading to neuromuscular paralysis [212]. Additionally, Shiga toxin produced by *E. coli* exacerbates neuroinflammation by increasing cytokine production, activating Toll-like receptors, and causing neuronal damage after crossing the BBB [213,214].

4.5. Foodborne Pathogens and BBB Disruption

BBB consists of endothelial cells joined by tight junctions (including claudins, occludin, and ZO-1). It is supported by pericytes, astrocytic end-feet, and the basement membrane, collectively forming the neurovascular unit (NVU). The NVU regulates the exchange of nutrients, metabolites, and immune cells between the circulation and the CNS, while also protecting the brain from toxins and pathogens. Multiple foodborne microbes have evolved mechanisms to breach the BBB, resulting in severe neurological conditions such as meningitis and encephalopathy. The principal pathways include: (i) lipopolysaccha-

ride (LPS)-mediated inflammation, whereby bacteria, such as *E. coli*, *Salmonella*, increase endothelial permeability and disrupt tight junctions [215,216]; (ii) transcellular and paracellular invasion, as demonstrated by *E. coli* K1 receptor-mediated transcytosis [217] and *L. monocytogenes* traversing between endothelial cells [218,219]; (iii) the "Trojan horse" mechanism, in which infected macrophages transport pathogens across the BBB, as observed with *Listeria* and *Salmonella* [186]; and (iv) direct endothelial interaction, exemplified by *Streptococcus suis* binding to host factors to penetrate the BBB [220].

Compromise of the BBB permits the infiltration of toxins, pathogens, and immune cells into the brain, which promotes neuroinflammation, neurodegeneration, and cognitive decline. Disruption of tight junction integrity initiates glial activation and the release of cytokines (TNF-α, IL-6, IL-1β), while oxidative stress and mitochondrial dysfunction further impair barrier function. Chronic foodborne infections can accelerate τ and β-amyloid accumulation in Alzheimer's disease [221,222], increase BBB permeability and α-synuclein aggregation in Parkinson's disease [223], and facilitate autoimmune responses such as demyelination in multiple sclerosis, as observed in *Campylobacter jejuni*–induced Guillain–Barré syndrome [224]. Comparable mechanisms may exacerbate vascular injury in stroke, amyotrophic lateral sclerosis (ALS), and other neurological disorders [225]. Collectively, these findings suggest that Gram-negative foodborne pathogens contribute to both gastrointestinal and chronic neurological diseases by disrupting the BBB and altering receptor interactions, underscoring the importance of preventive strategies. Table 9 summarizes the pathogens involved in CNS and neurodegenerative diseases.

Table 9. List of some pathogens involved in CNS and neurodegenerative diseases.

Bacterium	Effect on CNS/Neurodegenerative
***E. coli* (EHEC, K1)**	Neuroinflammation, oxidative stress, and neuronal injury. Contributes to Alzheimer's (amyloid-β accumulation) and Parkinson's (α-synuclein aggregation) [186,202–204,213–215,217,221,223,226]
S. enterica	Cognitive decline and neurodegeneration due to chronic inflammation. May exacerbate Alzheimer's- or Parkinson-like pathology through endotoxin exposure and α-synuclein aggregation [205,206,215,216,218,219,223]
L. monocytogenes	Causes meningitis, meningoencephalitis, encephalitis. Leads to chronic neuroinflammation, neuronal degeneration, and BBB disruption [199,207,211,218,219]
C. botulinum	Neurotoxicity, neuromuscular paralysis, and possible contribution to chronic neurodegenerative conditions (by altering gut–brain axis). [208,212]
Streptococcus suis	Induces bacterial meningitis and neuroinflammation [220]
C. jejuni	Associated with Guillain–Barré Syndrome (GBS) and potentially with multiple sclerosis (MS)-like pathology [224]

4.6. Role of Polyphenols and Their Metabolites in Central Nervous System Protection

Disruption of BBB, frequently initiated by pathogenic agents, contributes to neurological disorders including Alzheimer's disease, Parkinson's disease, multiple sclerosis, and Huntington's disease. These conditions are characterized by protein aggregation, mitochondrial dysfunction, oxidative stress, and neuroinflammation [225–227]. Native polyphenols exhibit limited central nervous system activity due to poor bioavailability and low BBB permeability. In contrast, microbial-derived metabolites such as urolithins,

phenyl-γ-valerolactones, and dihydroxylated phenolic acids demonstrate greater stability, enhanced absorption, and improved BBB penetration [228]. These metabolites reinforce tight junction integrity, attenuate oxidative and inflammatory stress, support mitochondrial quality control, and regulate proteostasis pathways [229,230]. Their colonic production and unique pharmacokinetic profiles contribute to the neuroprotective effects observed with polyphenol-rich diets, highlighting the microbiota as a critical mediator between nutrition and brain health. Metabolites, including urolithin A, phenyl-γ-valerolactones, and dihydroxylated phenylacetic acids, are capable of crossing the BBB, modulating neurocognitive pathways, and exhibiting antibacterial activity against foodborne pathogens. The combined antimicrobial and neuroprotective properties of these compounds may contribute to the prevention or mitigation of central nervous system disorders.

4.7. Core Neuroprotective Mechanisms

Anti-inflammatory and antioxidant actions. Both conjugated and free microbial phenolic acids, including 3,4-dihydroxyphenylacetic acid, protocatechuic acid, and dihydrocaffeic acid, as well as their sulfate and glucuronide conjugates, protect human neuronal (SH-SY5Y) cells from LPS- or t-BHP-induced injury. These compounds attenuate reactive oxygen species (ROS) and reduce cytokine production in macrophage and microglial models. Phase-II conjugates often demonstrate greater efficacy at physiologically relevant concentrations [231].

Proteostasis and aggregate toxicity. Phenyl-γ-valerolactones (PVLs)—signature colonic metabolites of flavan-3-ols—modulate cellular proteolytic systems and lower Aβ1-42 levels in neuronal cells; related PVLs selectively detoxify Aβ oligomers and prevent memory impairment in an AD mouse model, pointing to aggregate-focused neuroprotection [230,232].

Mitochondrial quality control (mitophagy) and cellular stress adaptation. Urolithin A acts as a potent inducer of mitophagy and cellular housekeeping pathways across multiple tissues. Preclinical studies in the central nervous system (CNS) demonstrate reduced neuroinflammation, improved blood–brain barrier (BBB) integrity, and protection against neuronal apoptosis following brain injury. These mechanisms are relevant to both acute and chronic neurodegenerative conditions [229,233].

Cerebrovascular function and BBB integrity. PVLs and related metabolites are associated with improved endothelial function and cerebral perfusion in both preclinical and translational studies. Urolithin A (UA) has been shown to directly preserve BBB structure and function in traumatic brain injury models. This mechanism is highly relevant to Alzheimer's disease and vascular cognitive impairment [229,233].

4.8. Alzheimer's Disease (AD)

BBB disruption and cerebrovascular dysfunction are now considered early hallmarks of AD. These processes contribute to impaired Aβ clearance and neuroinflammation [234]. Microbial polyphenol metabolites influence several AD-relevant pathways. Phenyl-γ-valerolactones (PVLs) reduce amyloid oligomer toxicity by binding to soluble Aβ species. They also support proteostasis by modulating the ubiquitin–proteasome system and autophagy. This lowers intracellular Aβ1-42 accumulation [230,232]. Urolithin A (UA) enhances autophagy and mitophagy, preserves mitochondrial function, and protects BBB integrity. In brain injury models, UA reduces apoptosis and counters AD-related vascular dysfunction [96,229]. Microbial phenolic acids (such as 3,4-dihydroxyphenylacetic and protocatechuic acid) decrease oxidative stress, microglial activation, and inflammatory cascades that drive Aβ aggregation and tau pathology [231]. Epidemiological studies link higher flavonol intake to reduced AD risk. Evidence suggests that gut-derived metabolites—not parent flavonoids—are the primary mediators, highlighting the impor-

tance of individual metabotypes [234]. While preclinical data are strong, clinical studies are lacking. No trials have tested purified polyphenol metabolites in AD, though early work on equol and UA shows feasibility. Future AD studies should stratify participants by metabotype, track metabolite exposure, and use neuroimaging and cognitive measures to clarify causality [235].

4.9. Parkinson's Disease (PD)

Microbial-derived polyphenol metabolites affect key PD processes. Urolithin A induces mitophagy, clearing dysfunctional mitochondria and reducing oxidative stress to support the survival of dopaminergic neurons [96]. PVLs enhance cellular proteostasis, reduce protein aggregation, and dampen oxidative and inflammatory responses, mechanisms relevant to both AD and PD [230]. Phenolic acids, including dihydrocaffeic acid and 3,4-dihydroxyphenylacetic acid, protect neurons by inhibiting microglial activation and oxidative injury and influence neurotransmitter metabolism and gut–brain signaling [231]. Epidemiological data link polyphenol-rich diets, such as the Mediterranean diet, to lower PD risk and slower progression. Neuroprotection largely depends on the gut microbiota's ability to generate UA, PVLs, and other metabolites, highlighting interindividual variability in metabolic responses [236].

4.10. Multiple Sclerosis (MS)

Polyphenol-derived microbial metabolites may modulate neuroinflammation in MS. Dihydrocaffeic and 3,4-dihydroxyphenylacetic acids reduce cytokine release, inhibit NF-κB, and limit oxidative stress in glial and immune cells, helping protect myelin and oligodendrocytes [231]. UA supports mitochondrial quality control and BBB integrity, which may enhance resilience to inflammation-induced neuronal damage [229]. Clinical data are lacking, but observational studies suggest that polyphenol-rich diets, such as the Mediterranean diet, may reduce relapse rates and disease progression, possibly through microbiota-dependent mechanisms [237].

4.11. Huntington's Disease (HD)

Polyphenol metabolites may alleviate HD pathology by reducing protein misfolding and mitochondrial dysfunction. PVLs enhance proteolytic systems and limit the accumulation of misfolded proteins [230]. UA promotes mitophagy, improves mitochondrial bioenergetics, and reduces ROS, countering neuronal vulnerability [116]. Microbial phenolic acids, with their antioxidant and anti-inflammatory properties, may also reduce excitotoxic and oxidative injury, which are central to HD progression.

4.12. Vascular Cognitive Impairment and Mixed Dementias

VCI, which often overlaps with AD, stems from cerebrovascular dysfunction that worsens cognitive decline [238]. Notably, microbial-derived polyphenol metabolites can support vascular and cognitive health via endothelial and anti-inflammatory effects. Specifically, phenolic acids (e.g., 3,4-dihydroxyphenylacetic, protocatechuic acid) improve endothelial function, reduce oxidative stress, and limit cytokine production [231]. Furthermore, urolithin A preserves BBB integrity and prevents neuronal apoptosis in ischemic injury models [229]. Similarly, equol, an isoflavone-derived metabolite, provides vasoprotective and neuroprotective benefits by modulating the ERβ receptor [235]. As a result, polyphenol-rich diets, such as the Mediterranean diet, are associated with a lower risk of vascular and mixed dementias, likely due to improved endothelial health and microbiota-driven metabolite production [239].

4.13. Anxiety and Mood Regulation

Microbiota-derived polyphenol metabolites influence emotional regulation and stress resilience. PVLs and dihydroresveratrol have anxiolytic and antidepressant-like effects in preclinical models. They improve behavioral test performance and normalize HPA axis activity, shown by reduced corticosterone levels [230,240]. These compounds increase the expression of GABA receptor subunits in the amygdala and hippocampus, thereby supporting inhibitory neurotransmission and enhancing stress resilience [241,242]. These metabolites also restore gut microbial diversity, reduce dysbiosis-related inflammation, and modulate neuroactive compounds such as tryptophan derivatives and short-chain fatty acids (SCFAs) [243–245]. Together, these findings suggest that the microbial products of catechins and resveratrol act through mechanisms that include modulation of the HPA axis, reinforcement of inhibitory neurotransmission, and gut–brain anti-inflammatory signaling, thereby helping to alleviate anxiety- and mood-related disturbances. While preclinical data are robust, human studies are limited, highlighting the need for biomarker-driven clinical trials.

4.14. Key Mechanisms of Neuroprotection by Polyphenol-Derived Metabolites

The neuroprotective effects of polyphenol-derived microbial metabolites are mediated through several mechanisms. These include inhibition of protein aggregation, restoration of mitochondrial quality control, attenuation of neuroinflammation, and reinforcement of antioxidant defenses.

- Mitochondrial Biogenesis and Autophagy Activation. Mitochondrial impairment and defective autophagy render neurons vulnerable, leading to energy failure and the formation of dysfunctional organelles. Polyphenol metabolites modulate mitochondrial quality control. Urolithin A activates PINK1/Parkin mitophagy to remove damaged mitochondria and stimulates PGC-1α-driven biogenesis, boosting ATP and reducing ROS. Increased LC3-II, BNIP3, and TFEB indicate greater lysosomal–autophagic flux. These effects prevent neuronal energy failure, key in early neurodegeneration [95,246].
- Inhibition of Amyloid and Protein Aggregation. Protein misfolding and aggregation are pivotal in the progression of Alzheimer's disease (AD) and Parkinson's disease (PD). Accumulation of amyloid-β (Aβ) fibrils or α-synuclein aggregates drives synaptic dysfunction and neuronal loss. Urolithin A Inhibits Aβ1–42 fibrillogenesis, destabilizes preformed fibrils, and reduces their cytotoxicity in neuronal cultures, while attenuating oligomer-mediated synaptic impairment in hippocampal neurons [234,246]. Urolithin B and dihydroresveratrol inhibit α-synuclein aggregation by interfering with hydrophobic interactions within the NAC (non-amyloid component) domain, thereby preventing the formation of toxic oligomers and promoting the proteasomal degradation of misfolded proteins [247–249].
- Modulation of neuroinflammation. Chronic neuroinflammation, driven by persistent activation of microglia and astrocytes, contributes to blood–brain barrier disruption and neuronal injury. Phenylacetic acid and phenylpropionic acid derivatives suppress IL-6, TNF-α, and IL-1β production in activated microglia, inhibit NF-κB translocation and MAPK phosphorylation, and promote a shift toward M2-like microglia expressing Arg1 and IL-10. This immunomodulatory effect reduces glial scarring, protects the BBB, and limits bystander neuronal damage [240,250].
- Antioxidant and Redox-Modulating Effects. Oxidative stress is a shared mechanism of neuronal injury in AD, PD, and related disorders. Excessive ROS and RNS damage lipids, proteins, and DNA, disrupting synaptic function. 3,4-Dihydroxyphenylacetic acid (DOPAC) and protocatechuic acid activate the Nrf2/ARE pathway, thereby upregulating HO-1, SOD1, and catalase, which in turn increase intracellular GSH

and reduce lipid hydroperoxide accumulation. These metabolites also stabilize the mitochondrial membrane potential (Δψm), lower mtROS production, and preserve synaptic plasticity and neurotransmitter balance [212,247,251,252].

Thus, in addition to their activity against foodborne pathogens, polyphenol-derived metabolites exert multitarget neuroprotective effects, including the following:

- ✔ Block amyloid and α-synuclein aggregation.
- ✔ Restore mitochondrial homeostasis through biogenesis and mitophagy.
- ✔ Reprogram neuroinflammation toward a protective phenotype.
- ✔ Reinforce endogenous antioxidant and redox-balancing systems.

This pleiotropic action profile underlines their therapeutic potential as next-generation neuroprotective agents in AD, PD, and other neurodegenerative conditions (Table 10, Figures 5 and 6).

Table 10. Neuroprotective Mechanisms of Polyphenol-Derived Metabolites.

Metabolite/Class	Mechanism of Action
Urolithin A (UA)	Inhibition of amyloid aggregation; synaptic protection [252]
Phenyl-γ-valerolactones (PVLs)	Proteostasis modulation; anti-amyloid oligomer detoxification [228,232]
Urolithin A (UA)	Mitophagy activation & mitochondrial biogenesis; BBB support [95,229,246]
Microbial phenolic acids (3,4-dihydroxyphenylacetic acid; protocatechuic; dihydrocaffeic; conjugates)	Anti-inflammatory & antioxidant actions [231]
Phenylacetic & phenylpropionic acid derivatives	Neuroinflammation modulation; microglial polarization [240,250]
DOPAC & Protocatechuic acid	Antioxidant/redox modulation [251]
PVLs & phenolic acids (vascular axis)	Endothelial/BBB support relevant to VCI [231,238]
Equol (microbiome derived ERβ agonist)	Vascular–cognitive aging; metabotype-aware translation [235]

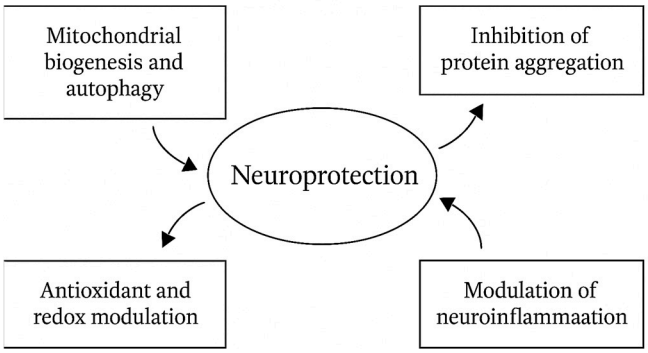

Figure 5. Schematic representation of the main mechanistic pathways through which polyphenol-derived metabolites exert neuroprotective effects. These include inhibition of protein aggregation, enhancement of antioxidant and redox responses, modulation of neuroinflammation, and stimulation of mitochondrial biogenesis and autophagy.

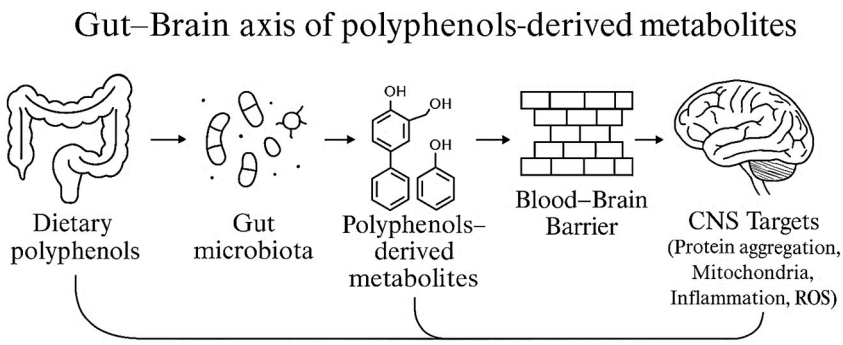

Figure 6. Overview of the gut–brain axis linking dietary polyphenols to brain health. After consuming polyphenol-rich foods, the gut microbiota converts parent compounds into bioactive metabolites (e.g., phenyl-γ-valerolactones, urolithins, dihydroresveratrol, protocatechuic acid, and DOPAC). These metabolites enter circulation, cross the blood–brain barrier, and act on key pathways of neurodegeneration—protein aggregation, mitochondrial dysfunction, neuroinflammation, and oxidative stress—thereby supporting neuroprotection, mood regulation, and reduced cognitive decline.

5. Critical Perspective and Limitations

Despite significant progress in understanding polyphenol metabolism by gut microbiota, the primary research gap is the limited understanding of how different human metabotypes consistently affect long-term health outcomes across populations. Several knowledge gaps persist in current research. The majority of studies employ in vitro assays or simplified microbial models, which fail to adequately represent the complex physicochemical and ecological environment of the human gut and its interactions with host tissues [48]. The dynamic processes of microbial biotransformation, instability of intermediate metabolites, and interindividual differences in gut metabotypes further hinder the establishment of causal relationships between dietary intake, metabolite production, and systemic effects [52]. Additionally, the influence of diet, lifestyle, and genetic factors on polyphenol metabolism and metabotype development remains largely unexplored. Furthermore, most studies have been conducted in vitro or using animal models, and additional human clinical trials are needed to validate the findings. Understanding the clinical implications of metabotypes can lead to improved dietary recommendations and therapeutic interventions tailored to individual metabotypes. Potential clinical applications include using metabotype information to enhance the efficacy of polyphenol-based supplements and designing personalized nutrition plans that optimize the health benefits of consuming polyphenol-rich foods. More research in these areas will facilitate the translation of basic science findings into actionable clinical practices. Analytical limitations also remain, as many low-molecular-weight phenolic metabolites are present at nanomolar concentrations and are challenging to detect or quantify accurately in biological fluids [253]. Additionally, most experimental designs do not assess multiple endpoints, such as anti-biofilm activity, gut barrier modulation, and neuronal protection, within a unified framework. This lack of integration limits a comprehensive understanding of their pleiotropic functions. To improve translational relevance, standardization of experimental protocols, adoption of advanced multi-omics approaches, and use of microfluidic and organoid-on-chip models that simulate the gut–brain axis are required [254,255]. Ultimately, rigorously controlled human intervention studies are necessary to confirm the physiological significance of microbial-derived polyphenol metabolites and to elucidate their dose–response relationships in vivo [51].

6. Conclusions and Future Directions

To advance the field, future research must address the experimental and methodological limitations previously outlined and engage directly with the practical translation of mechanistic knowledge into clinical and nutritional frameworks. Specifically, investigations should prioritize elucidating the host and microbial factors that modulate the metabolism and bioactivity of dietary polyphenols. Given that gut microbiota converts polyphenols into a range of low-molecular-weight metabolites—including urolithins, valerolactones, phenolic acids, and dihydroresveratrol—which possess greater stability, enhanced bioavailability, and increased biological activity compared to their parent compounds, it is critically important to delineate the specific microbiota profiles and metabolic pathways responsible for these transformations. This knowledge will inform the design of personalized nutritional strategies and interventions, such as microbiota-informed dietary recommendations that consider an individual's metabotype, genetic background, and habitual dietary intake. Moreover, future studies should rigorously evaluate the efficacy of innovative delivery systems, including synbiotic formulations, nanoencapsulated polyphenols, and targeted delivery mechanisms, in optimizing colonic bioavailability and therapeutic outcomes in both infectious and neurodegenerative conditions. By focusing on the pathways and clinical implications of polyphenol-derived metabolites, research can provide robust evidence to guide the development of next-generation nutraceuticals and adjunct therapies. This approach holds significant potential to address urgent health concerns such as antimicrobial resistance, gut dysbiosis, and neurodegenerative diseases, ultimately facilitating the integration of polyphenol research into precision medicine and public health policy.

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References

1. Santhiravel, S.; Bekhit, A.E.-D.A.; Mendis, E.; Jacobs, J.L.; Dunshea, F.R.; Rajapakse, N.; Ponnampalam, E.N. The impact of plant phytochemicals on the gut microbiota of humans for a balanced life. *Int. J. Mol. Sci.* **2022**, *23*, 8124. [CrossRef]
2. Scalbert, A.; Williamson, G. Dietary intake and bioavailability of polyphenols. *J. Nutr.* **2000**, *130*, 2073S–2085S. [CrossRef]
3. Mosele, J.I.; Macià, A.; Motilva, M.-J. Metabolic and microbial modulation of the large intestine ecosystem by non-absorbed diet phenolic compounds: A review. *Molecules* **2015**, *20*, 17429–17468. [CrossRef] [PubMed]
4. Cai, Y.; Xu, J.; Wang, B. Gut Microbiota-Targeted Polyphenol Interventions: A Novel Paradigm and Synergistic Strategies for Obesity Management. *Phytother. Res.* **2025**, *39*, 4913–4933. [CrossRef] [PubMed]
5. Gonzalez-Gomez, Á.; Cantone, M.; Garcia-Muñoz, A.M.; Victoria-Montesinos, D.; Lucas-Abellán, C.; Serrano-Martínez, A.; Muñoz-Morillas, A.M.; Morillas-Ruiz, J.M. Effect of Polyphenol-Rich Interventions on Gut Microbiota and Inflammatory or Oxidative Stress Markers in Adults Who Are Overweight or Obese: A Systematic Review and Meta-Analysis. *Nutrients* **2025**, *17*, 2468. [CrossRef]
6. Davidova, S.; Galabov, A.S.; Satchanska, G. Antibacterial, antifungal, antiviral activity, and mechanisms of action of plant polyphenols. *Microorganisms* **2024**, *12*, 2502. [CrossRef] [PubMed]

7. Jadaun, S.; Sharma, U.; Khapudang, R.; Siddiqui, S. Polyphenolic Compounds from Diet: Potential Role in Regulation of Gut Microbiota and Effects on Human Body. In *Sustainable Food Systems (Volume I) SFS: Framework, Sustainable Diets, Traditional Food Culture & Food Production*; Springer: Berlin/Heidelberg, Germany, 2024; pp. 275–296.
8. Ávila-Gálvez, M.Á.; Garay-Mayol, B.; Marín, A.; Brito, M.A.; Giménez-Bastida, J.A.; Espín, J.C.; González-Sarrías, A. Metabolic Profiling of a Mediterranean-Inspired (Poly) phenol-Rich Mixture in the Brain: Perfusion Effect and In Vitro Blood– Brain Barrier Transport Validation. *J. Agric. Food Chem.* **2025**, *73*, 11056–11066. [CrossRef]
9. Tavan, M.; Hanachi, P.; de la Luz Cádiz-Gurrea, M.; Segura Carretero, A.; Mirjalili, M.H. Natural phenolic compounds with neuroprotective effects. *Neuroch. Res.* **2024**, *49*, 306–326. [CrossRef]
10. Li, W.; Chen, H.; Xu, B.; Wang, Y.; Zhang, C.; Cao, Y.; Xing, X. Research progress on classification, sources and functions of dietary polyphenols for prevention and treatment of chronic diseases. *J. Fut. Foods* **2023**, *3*, 289–305. [CrossRef]
11. Shahidi, F.; Yeo, J. Bioactivities of phenolics by focusing on suppression of chronic diseases: A review. *Int. J. Mol. Sci.* **2018**, *19*, 1573. [CrossRef]
12. Diwan, A.; Panche, A. Flavonoids: An overview. *J. Nutr. Sci.* **2016**, *5*, e47. [CrossRef]
13. Baur, J.A.; Sinclair, D.A. Therapeutic potential of resveratrol: The in vivo evidence. *Nat. Rev. Drug Discov.* **2006**, *5*, 493–506. [CrossRef] [PubMed]
14. Landete, J.M. Plant and mammalian lignans: A review of source, intake, metabolism, intestinal bacteria and health. *Food Res. Int.* **2012**, *46*, 410–424. [CrossRef]
15. Quideau, S.; Deffieux, D.; Douat-Casassus, C.; Pouységu, L. Plant polyphenols: Chemical properties, biological activities, and synthesis. *Angewandte Chemie Int. Edit.* **2011**, *50*, 586–621. [CrossRef]
16. Kiokias, S.; Oreopoulou, V. A review of the health protective effects of phenolic acids against a range of severe pathologic conditions (including coronavirus-based infections). *Molecules* **2021**, *26*, 5405. [CrossRef]
17. Rathod, N.B.; Elabed, N.; Punia, S.; Ozogul, F.; Kim, S.-K.; Rocha, J.M. Recent developments in polyphenol applications on human health: A review with current knowledge. *Plants* **2023**, *12*, 1217. [CrossRef] [PubMed]
18. Teka, T.; Zhang, L.; Ge, X.; Li, Y.; Han, L.; Yan, X. Stilbenes: Source plants, chemistry, biosynthesis, pharmacology, application and problems related to their clinical application-A comprehensive review. *Phytochem.* **2022**, *197*, 113128. [CrossRef]
19. Rodríguez-García, C.; Sánchez-Quesada, C.; Toledo, E.; Delgado-Rodríguez, M.; Gaforio, J.J. Naturally lignan-rich foods: A dietary tool for health promotion? *Molecules* **2019**, *24*, 917. [CrossRef]
20. Perez-Jimenez, J.; Neveu, V.; Vos, F.; Scalbert, A. Systematic analysis of the content of 502 polyphenols in 452 foods and beverages: An application of the phenol-explorer database. *J. Agric. Food Chem.* **2010**, *58*, 4959–4969. [CrossRef]
21. Manach, C.; Scalbert, A.; Morand, C.; Rémésy, C.; Jiménez, L. Polyphenols: Food sources and bioavailability. *Am. J. Clin. Nutr.* **2004**, *79*, 727–747. [CrossRef]
22. Pinasseau, L.; Vallverdú-Queralt, A.; Verbaere, A.; Roques, M.; Meudec, E.; Le Cunff, L.; Péros, J.-P.; Ageorges, A.; Sommerer, N.; Boulet, J.-C. Cultivar diversity of grape skin polyphenol composition and changes in response to drought investigated by LC-MS based metabolomics. *Front. Plant Sci.* **2017**, *8*, 1826. [CrossRef]
23. Vermerris, W.; Nicholson, R. *Phenolic Compound Biochemistry*; Springer Science & Business Media: Berlin/Heidelberg, Germany, 2007.
24. Muñoz-Ulecia, E.; Bernués, A.; Ondé, D.; Ramanzin, M.; Soliño, M.; Sturaro, E.; Martín-Collado, D. People' s attitudes towards the agrifood system influence the value of ecosystem services of mountain agroecosystems. *Plos ONE* **2022**, *17*, e0267799. [CrossRef] [PubMed]
25. D' Archivio, M.; Filesi, C.; Di Benedetto, R.; Gargiulo, R.; Giovannini, C.; Masella, R. Polyphenols, dietary sources and bioavailability. *Annali-Istituto Superiore di Sanità* **2007**, *43*, 348.
26. Fabbrini, M.; D'Amico, F.; Barone, M.; Conti, G.; Mengoli, M.; Brigidi, P.; Turroni, S. Polyphenol and tannin nutraceuticals and their metabolites: How the human gut microbiota influences their properties. *Biomolecules* **2022**, *12*, 875. [CrossRef]
27. Prakash, V.; Bose, C.; Sunilkumar, D.; Cherian, R.M.; Thomas, S.S.; Nair, B.G. Resveratrol as a promising nutraceutical: Implications in gut microbiota modulation, inflammatory disorders, and colorectal cancer. *Int. J. Mol. Sci.* **2024**, *25*, 3370. [CrossRef]
28. Akinwumi, B.C.; Bordun, K.-A.M.; Anderson, H.D. Biological activities of stilbenoids. *Int. J. Mol. Sci.* **2018**, *19*, 792. [CrossRef] [PubMed]
29. Kaşıkcı, M.B.; Bağdatlıoğlu, N. Bioavailability of quercetin. *Curr. Res. Nutr. Food Sci.* **2016**, *4*, 146–151. [CrossRef]
30. Baldi, S.; Tristán Asensi, M.; Pallecchi, M.; Sofi, F.; Bartolucci, G.; Amedei, A. Interplay between lignans and gut microbiota: Nutritional, functional and methodological aspects. *Molecules* **2023**, *28*, 343. [CrossRef]
31. Smeriglio, A.; Barreca, D.; Bellocco, E.; Trombetta, D. Proanthocyanidins and hydrolysable tannins: Occurrence, dietary intake and pharmacological effects. *Brit. J. Pharmacol.* **2017**, *174*, 1244–1262. [CrossRef]
32. Kawabata, K.; Yoshioka, Y.; Terao, J. Role of intestinal microbiota in the bioavailability and physiological functions of dietary polyphenols. *Molecules* **2019**, *24*, 370. [CrossRef]

33. Mena, P.; Bresciani, L.; Brindani, N.; Ludwig, I.A.; Pereira-Caro, G.; Angelino, D.; Llorach, R.; Calani, L.; Brighenti, F.; Clifford, M.N. Phenyl-γ-valerolactones and phenylvaleric acids, the main colonic metabolites of flavan-3-ols: Synthesis, analysis, bioavailability, and bioactivity. *Nat. Prod. Rep.* **2019**, *36*, 714–752. [CrossRef]
34. Rodríguez-Daza, M.C.; Pulido-Mateos, E.C.; Lupien-Meilleur, J.; Guyonnet, D.; Desjardins, Y.; Roy, D. Polyphenol-mediated gut microbiota modulation: Toward prebiotics and further. *Front. Nutr.* **2021**, *8*, 689456. [CrossRef]
35. Caballero Fernández, V.; Estévez García, M.; Tomás Barberán, F.A.; Morcuende Sánchez, D.; Martín Tornero, I.; Delgado Perón, J. Biodegradation of Punicalagin into ellagic acid by selected probiotic bacteria: A study of the underlying mechanisms by MS-Based proteomics. *J. Agric. Food Chem.* **2022**, *70*, 16273–16285. [CrossRef]
36. Hassan, M.H.U.; Shahbaz, M.; Momal, U.; Naeem, H.; Imran, M.; Abdelgawad, M.A.; Ghoneim, M.M.; Mostafa, E.M.; El-Ghorab, A.H.; Alsagaby, S.A. Exploring Punicalagin Potential Against Cancers: A Comprehensive Review. *Food Sci. Nutr.* **2025**, *13*, e70072. [CrossRef] [PubMed]
37. García-Villalba, R.; Beltrán, D.; Frutos, M.D.; Selma, M.V.; Espín, J.C.; Tomás-Barberán, F.A. Metabolism of different dietary phenolic compounds by the urolithin-producing human-gut bacteria *Gordonibacter urolithinfaciens* and *Ellagibacter isourolithinifaciens*. *Food Funct.* **2020**, *11*, 7012–7022. [CrossRef] [PubMed]
38. da, C.; Pinaffi-Langley, A.C.; Tarantini, S.; Hord, N.G.; Yabluchanskiy, A. Polyphenol-derived microbiota metabolites and cardiovascular health: A concise review of human studies. *Antioxidants* **2024**, *13*, 1552.
39. La Rosa, G.; Lonardo, M.S.; Cacciapuoti, N.; Muscariello, E.; Guida, B.; Faraonio, R.; Santillo, M.; Damiano, S. Dietary polyphenols, microbiome, and multiple sclerosis: From molecular anti-inflammatory and neuroprotective mechanisms to clinical evidence. *Int. J. Mol. Sci.* **2023**, *24*, 7247. [CrossRef]
40. Tremaroli, V.; Bäckhed, F. Functional interactions between the gut microbiota and host metabolism. *Nature* **2012**, *489*, 242–249. [CrossRef]
41. Moco, S.; Martin, F.-P.J.; Rezzi, S. Metabolomics view on gut microbiome modulation by polyphenol-rich foods. *J. Proteome Res.* **2012**, *11*, 4781–4790. [CrossRef] [PubMed]
42. Favari, C.; de Alvarenga, J.F.R.; Sánchez-Martínez, L.; Tosi, N.; Mignogna, C.; Cremonini, E.; Manach, C.; Bresciani, L.; Del Rio, D.; Mena, P. Factors driving the inter-individual variability in the metabolism and bioavailability of (poly) phenolic metabolites: A systematic review of human studies. *Redox Biol.* **2024**, *71*, 103095. [CrossRef]
43. Dong, X.; Bae, M.; Le, C.; Aguilar Ramos, M.A.; Balskus, E.P. Enantiocomplementary Gut Bacterial Enzymes Metabolize Dietary Polyphenols. *J. Am. Chem. Soc.* **2025**, *147*, 7231–7244. [CrossRef] [PubMed]
44. Stevens, J.F.; Maier, C.S. The chemistry of gut microbial metabolism of polyphenols. *Phytochem. Rev.* **2016**, *15*, 425–444. [CrossRef]
45. Duda-Chodak, A.; Tarko, T.; Satora, P.; Sroka, P. Interaction of dietary compounds, especially polyphenols, with the intestinal microbiota: A review. *Eur. J. Nutr.* **2015**, *54*, 325–341. [CrossRef]
46. Tomás-Barberán, F.A.; Selma, M.V.; Espin, J.C. Interactions of gut microbiota with dietary polyphenols and consequences to human health. *Curr. Opin. Clin. Nutr. Metab. Care* **2016**, *19*, 471–476. [CrossRef]
47. Kim, Y.J.; Jung, J.; Kim, D.H. Gut microbiota-mediated biotransformation of polyphenols: Recent advances and future perspectives. *Food Res. Int.* **2023**, *167*, 112675.
48. Selma, M.V.; Espin, J.C.; Tomas-Barberan, F.A. Interaction between phenolics and gut microbiota: Role in human health. *J. Agric. Food Chem.* **2009**, *57*, 6485–6501. [CrossRef] [PubMed]
49. Mena, P.; de Llano, D.G.; Brindani, N.; Esteban-Fernández, A.; Curti, C.; Moreno-Arribas, M.V.; Del Rio, D.; Bartolomé, B. 5-(3′, 4′-Dihydroxyphenyl)-γ-valerolactone and its sulphate conjugates, representative circulating metabolites of flavan-3-ols, exhibit anti-adhesive activity against uropathogenic *Escherichia coli* in bladder epithelial cells. *J. Funct. Foods* **2017**, *29*, 275–280. [CrossRef]
50. Espin, J.C.; Larrosa, M.; García-Conesa, M.T.; Tomás-Barberán, F. Biological significance of urolithins, the gut microbial ellagic acid-derived metabolites: The evidence so far. *Evidence-Based Compl. Altern. Med.* **2013**, *2013*, 270418. [CrossRef]
51. Espin, J.C.; Gonzalez-Sarrias, A.; Tomas-Barberan, F.A. The gut microbiota: A key factor in the therapeutic effects of (poly) phenols. *Biochem. Pharmacol.* **2017**, *139*, 82–93. [CrossRef]
52. Cardona, F.; Andrés-Lacueva, C.; Tulipani, S.; Tinahones, F.J.; Queipo-Ortuño, M.I. Benefits of polyphenols on gut microbiota and implications in human health. *J. Nutr. Biochem.* **2013**, *24*, 1415–1422. [CrossRef]
53. Aura, A.-M. Microbial metabolism of dietary phenolic compounds in the colon. *Phytochem. Rev.* **2008**, *7*, 407–429. [CrossRef]
54. Bode, L.M.; Bunzel, D.; Huch, M.; Cho, G.-S.; Ruhland, D.; Bunzel, M.; Bub, A.; Franz, C.M.; Kulling, S.E. In vivo and in vitro metabolism of trans-resveratrol by human gut microbiota. *Am. J. Clin. Nutr.* **2013**, *97*, 295–309. [CrossRef] [PubMed]
55. Clavel, T.; Henderson, G.; Alpert, C.A.; Philippe, C.; Rigottier-Gois, L.; Doré, J.; Blaut, M. Intestinal bacterial communities that produce active estrogen-like compounds enterodiol and enterolactone in humans. *Appl. Environ. Microbiol* **2005**, *71*, 6077–6085. [CrossRef]
56. Landete, J. Ellagitannins, ellagic acid and their derived metabolites: A review about source, metabolism, functions and health. *Food Res. Int.* **2011**, *44*, 1150–1160. [CrossRef]

57. Mingshu, L.; Kai, Y.; Qiang, H.; Dongying, J. Biodegradation of gallotannins and ellagitannins. *J. Basic Microbiol.* **2006**, *46*, 68–84. [CrossRef]
58. Piwowarski, J.P.; Stanisławska, I.; Granica, S.; Stefańska, J.; Kiss, A.K. Phase II conjugates of urolithins isolated from human urine and potential role of β -glucuronidases in their disposition. *Drug Met. Disp.* **2017**, *45*, 657–665. [CrossRef]
59. Feng, W.; Liu, J.; Cheng, H.; Zhang, D.; Tan, Y.; Peng, C. Dietary compounds in modulation of gut microbiota-derived metabolites. *Front. Nutr.* **2022**, *9*, 939571. [CrossRef]
60. Speckmann, B.; Ehring, E.; Hu, J.; Rodriguez Mateos, A. Exploring substrate–microbe interactions: A metabiotic approach toward developing targeted synbiotic compositions. *Gut Microbes* **2024**, *16*, 2305716. [CrossRef] [PubMed]
61. Martinelli, F.; Thiele, I. Microbial metabolism marvels: A comprehensive review of microbial drug transformation capabilities. *Gut Microbes* **2024**, *16*, 2387400. [CrossRef]
62. Selma, M.V.; Beltrán, D.; García-Villalba, R.; Espín, J.C.; Tomás-Barberán, F.A. Description of urolithin production capacity from ellagic acid of two human intestinal *Gordonibacter* species. *Food Funct.* **2014**, *5*, 1779–1784. [CrossRef] [PubMed]
63. Beltrán, D.; Romo-Vaquero, M.; Espín, J.C.; Tomás-Barberán, F.A.; Selma, M.V. *Ellagibacter isourolithinifaciens* gen. nov., sp. nov., a new member of the family *Eggerthellaceae*, isolated from human gut. *Int. J. Syst. Evol. Microbiol.* **2018**, *68*, 1707–1712.
64. Kipshidze, M. Age-Related Changes in Proportions of Urolithins A, B, and 0. *Junior Res.* **2023**, *1*, 17–29. [CrossRef]
65. Monagas, M.; Urpi-Sarda, M.; Sánchez-Patán, F.; Llorach, R.; Garrido, I.; Gómez-Cordovés, C.; Andres-Lacueva, C.; Bartolomé, B. Insights into the metabolism and microbial biotransformation of dietary flavan-3 -ols and the bioactivity of their metabolites. *Food Funct.* **2010**, *1*, 233–253. [CrossRef] [PubMed]
66. Chourasia, R.; Phukon, C.L.; Abedin, M.M.; Sahoo, D.; Rai, A.K. Microbial Transformation during Gut Fermentation. In *Bioactive Compounds in Fermented Foods*; CRC Press: Boca Raton, FL, USA, 2021; pp. 365–402.
67. Wang, M.; Li, J.; Hu, T.; Zhao, H. Metabolic fate of tea polyphenols and their crosstalk with gut microbiota. *Food Sci. Hum. Wellness* **2022**, *11*, 455–466. [CrossRef]
68. Hidalgo, M.; Oruna-Concha, M.J.; Kolida, S.; Walton, G.E.; Kallithraka, S.; Spencer, J.P.; de Pascual-Teresa, S. Metabolism of anthocyanins by human gut microflora and their influence on gut bacterial growth. *J. Agric. Food Chem.* **2012**, *60*, 3882–3890. [CrossRef]
69. Gade, A.; Kumar, M.S. Gut microbial metabolites of dietary polyphenols and their potential role in human health and diseases. *J. Physiol. Biochem.* **2023**, *79*, 695–718. [CrossRef]
70. Sallam, I.E.; Abdelwareth, A.; Attia, H.; Aziz, R.K.; Homsi, M.N.; von Bergen, M.; Farag, M.A. Effect of gut microbiota biotransformation on dietary tannins and human health implications. *Microorganisms* **2021**, *9*, 965. [CrossRef]
71. Le Sayec, M.; Xu, Y.; Laiola, M.; Gallego, F.A.; Katsikioti, D.; Durbidge, C.; Kivisild, U.; Armes, S.; Lecomte, M.; Fança-Berthon, P. The effects of Aronia berry (poly) phenol supplementation on arterial function and the gut microbiome in middle aged men and women: Results from a randomized controlled trial. *Clin. Nutr.* **2022**, *41*, 2549–2561. [CrossRef]
72. Loo, Y.T.; Howell, K.; Chan, M.; Zhang, P.; Ng, K. Modulation of the human gut microbiota by phenolics and phenolic fiber-rich foods. *Compr. Rev. Food Sci. Food Safety* **2020**, *19*, 1268–1298. [CrossRef] [PubMed]
73. Istas, G.; Wood, E.; Le Sayec, M.; Rawlings, C.; Yoon, J.; Dandavate, V.; Cera, D.; Rampelli, S.; Costabile, A.; Fromentin, E. Effects of aronia berry (poly) phenols on vascular function and gut microbiota: A double-blind randomized controlled trial in adult men. *Am. J. Clin. Nutr.* **2019**, *110*, 316–329. [CrossRef]
74. Selma, M.V.; Tomás-Barberán, F.A.; Romo-Vaquero, M.; Cortés-Martín, A.; Espín, J.C. Understanding polyphenols' health effects through the gut microbiota. In *Dietary Polyphenols: Their Metabolism and Health Effects*; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 2020; pp. 497–531.
75. Ortiz, C.; Manta, B. Advances in equol production: Sustainable strategies for unlocking soy isoflavone benefits. *Results Chem.* **2024**, *7*, 101288. [CrossRef]
76. Kim, M.; Kim, S.-I.; Han, J.; Wang, X.-L.; Song, D.-G.; Kim, S.-U. Stereospecific biotransformation of dihydrodaidzein into (3 S)-equol by the human intestinal bacterium *Eggerthella* strain Julong 732. *Appl. Environ. Microbiol.* **2009**, *75*, 3062–3068. [CrossRef] [PubMed]
77. Landete, J.M.; Arqués, J.; Medina, M.; Gaya, P.; De Las Rivas, B.; Muñoz, R. Bioactivation of phytoestrogens: Intestinal bacteria and health. *Crit. Rev. Food Sci. Nutr.* **2016**, *56*, 1826–1843. [CrossRef]
78. Clavel, T.; Borrmann, D.; Braune, A.; Doré, J.; Blaut, M. Occurrence and activity of human intestinal bacteria involved in the conversion of dietary lignans. *Anaerobe* **2006**, *12*, 140–147. [CrossRef]
79. Li, Y.; Wang, F.; Li, J.; Ivey, K.L.; Wilkinson, J.E.; Wang, D.D.; Li, R.; Liu, G.; Eliassen, H.A.; Chan, A.T. Dietary lignans, plasma enterolactone levels, and metabolic risk in men: Exploring the role of the gut microbiome. *BMC Microbiol.* **2022**, *22*, 82. [CrossRef] [PubMed]
80. Peirotén, Á.; Gaya, P.; Álvarez, I.; Bravo, D.; Landete, J.M. Influence of different lignan compounds on enterolignan production by Bifidobacterium and Lactobacillus strains. *Int. J. Food Microbiol.* **2019**, *289*, 17–23. [CrossRef]

81. Cueva, C.; Moreno-Arribas, M.V.; Martín-Álvarez, P.J.; Bills, G.; Vicente, M.F.; Basilio, A.; Rivas, C.L.; Requena, T.; Rodríguez, J.M.; Bartolomé, B. Antimicrobial activity of phenolic acids against commensal, probiotic and pathogenic bacteria. *Res. Microbiol.* **2010**, *161*, 372–382. [CrossRef]
82. Kiriyama, Y.; Tokumaru, H.; Sadamoto, H.; Kobayashi, S.; Nochi, H. Effects of phenolic acids produced from food-derived flavonoids and amino acids by the gut microbiota on health and disease. *Molecules* **2024**, *29*, 5102. [CrossRef]
83. Kan, J.; Wu, F.; Wang, F.; Zheng, J.; Cheng, J.; Li, Y.; Yang, Y.; Du, J. Phytonutrients: Sources, bioavailability, interaction with gut microbiota, and their impacts on human health. *Front. Nutr.* **2022**, *9*, 960309. [CrossRef]
84. Moens, E.; Bolca, S.; Van de Wiele, T.; Van Landschoot, A.; Goeman, J.L.; Possemiers, S.; Verstraete, W. Exploration of isoxanthohumol bioconversion from spent hops into 8 -prenylnaringenin using resting cells of *Eubacterium limosum*. *AMB Express* **2020**, *10*, 79. [CrossRef] [PubMed]
85. Possemiers, S.; Rabot, S.; Espín, J.C.; Bruneau, A.; Philippe, C.; González-Sarrías, A.; Heyerick, A.; Tomás-Barberán, F.A.; De Keukeleire, D.; Verstraete, W. *Eubacterium limosum* activates isoxanthohumol from hops (*Humulus lupulus* L.) into the potent phytoestrogen 8-prenylnaringenin in vitro and in rat intestine. *J. Nutr.* **2008**, *138*, 1310–1316. [CrossRef]
86. Kwon, C.; Ediriweera, M.K.; Kim Cho, S. Interplay between phytochemicals and the colonic microbiota. *Nutrients* **2023**, *15*, 1989. [CrossRef] [PubMed]
87. Lee, H.C.; Jenner, A.M.; Low, C.S.; Lee, Y.K. Effect of tea phenolics and their aromatic fecal bacterial metabolites on intestinal microbiota. *Res. Microbiol.* **2006**, *157*, 876–884. [CrossRef]
88. Wang, X.; Qi, Y.; Zheng, H. Dietary polyphenol, gut microbiota, and health benefits. *Antioxidants* **2022**, *11*, 1212. [CrossRef] [PubMed]
89. Zhao, Q.; Wang, Z.; Wang, X.; Yan, X.; Guo, Q.; Yue, Y.; Yue, T.; Yuan, Y. The bioaccessibility, bioavailability, bioactivity, and prebiotic effects of phenolic compounds from raw and solid-fermented mulberry leaves during in vitro digestion and colonic fermentation. *Food Res. Int.* **2023**, *165*, 112493. [CrossRef]
90. Makarewicz, M.; Drozdz, I.; Tarko, T.; Duda-Chodak, A. The interactions between polyphenols and microorganisms, especially gut microbiota. *Antioxidants* **2021**, *10*, 188. [CrossRef]
91. Dokic, J.; Dinic, M.; Sokovic Bajic, S.; Bisenic, A.; Mitrovic, H.; Jakovljevic, S.; Radojevic, D.; Brdaric, E.; Lukic, J.; Zivkovic, M. High-throughput workflow for cultivation and characterization of gut microbiota strains with anti-inflammatory properties and metabolite signature associated with gut-brain communication. *Sci. Rep.* **2025**, *15*, 8741. [CrossRef]
92. Hu, J.; Chen, J.; Xu, X.; Hou, Q.; Ren, J.; Yan, X. Gut microbiota-derived 3 -phenylpropionic acid promotes intestinal epithelial barrier function via *AhR* signaling. *Microbiome* **2023**, *11*, 102.
93. Elkhalifa, M.E.; Ashraf, M.; Ahmed, A.; Usman, A.; Hamdoon, A.A.; Elawad, M.A.; Almalki, M.G.; Mosa, O.F.; Niyazov, L.N.; Ayaz, M. Polyphenols and their nanoformulations as potential antibiofilm agents against multidrug-resistant pathogens. *Fut. Microbiol.* **2024**, *19*, 255–279. [CrossRef]
94. Alvarez-Martinez, F.J.; Barrajon-Catalan, E.; Encinar, J.A.; Rodriguez-Diaz, J.C.; Micol, V. Antimicrobial capacity of plant polyphenols against gram-positive bacteria: A comprehensive review. *Curr. Med. Chem.* **2020**, *27*, 2576–2606. [CrossRef]
95. Ryu, D.; Mouchiroud, L.; Andreux, P.A.; Katsyuba, E.; Moullan, N.; Nicolet-dit-Félix, A.A.; Williams, E.G.; Jha, P.; Lo Sasso, G.; Huzard, D. Urolithin A induces mitophagy and prolongs lifespan in *C. elegans* and increases muscle function in rodents. *Nat. Med.* **2016**, *22*, 879–888. [PubMed]
96. Zhang, Q.; Zhang, W.; Yuan, X.; Peng, X.; Hu, G. Urolithin A in Central Nervous System Disorders: Therapeutic Applications and Challenges. *Biomedicines* **2025**, *13*, 1553. [CrossRef] [PubMed]
97. Lavefve, L.; Howard, L.R.; Carbonero, F. Berry polyphenols metabolism and impact on human gut microbiota and health. *Food Funct.* **2020**, *11*, 45–65. [CrossRef]
98. Zhang, M.; Cui, S.; Mao, B.; Zhang, Q.; Zhao, J.; Zhang, H.; Tang, X.; Chen, W. Ellagic acid and intestinal microflora metabolite urolithin A: A review on its sources, metabolic distribution, health benefits, and biotransformation. *Crit. Rev. Food Sci. Nutr.* **2023**, *63*, 6900–6922. [CrossRef]
99. Del Rio, D.; Rodriguez-Mateos, A.; Spencer, J.P.; Tognolini, M.; Borges, G.; Crozier, A. Dietary (poly) phenolics in human health: Structures, bioavailability, and evidence of protective effects against chronic diseases. *Antioxid. Redox Signal.* **2013**, *18*, 1818–1892. [CrossRef]
100. Zhou, M.; Pang, X.E. Polyphenols and miRNA interplay: A novel approach to combat apoptosis and inflammation in Alzheimer's disease. *Front. Aging Neurosci.* **2025**, *17*, 1571563. [CrossRef]
101. Mitrea, L.; Nemeş, S.-A.; Szabo, K.; Teleky, B.-E.; Vodnar, D.C. Guts imbalance imbalances the brain: A review of gut microbiota association with neurological and psychiatric disorders. *Front. Med.* **2022**, *9*, 813204. [CrossRef] [PubMed]
102. Petersen, K.; Mansell, T.J. Unveiling the prebiotic potential of polyphenols in gut health and metabolism. *Curr. Opin. Biotech.* **2025**, *95*, 103338. [CrossRef]
103. Nemzer, B.V.; Al-Taher, F.; Kalita, D.; Yashin, A.Y.; Yashin, Y.I. Health-improving effects of polyphenols on the human intestinal microbiota: A review. *Int. J. Mol. Sci.* **2025**, *26*, 1335. [CrossRef]

104. Gonzalez-Sarrias, A.; Espin-Aguilar, J.C.; Romero-Reyes, S.; Puigcerver, J.; Alajarin, M.; Berna, J.; Selma, M.V.; Espin, J.C. Main determinants affecting the antiproliferative activity of stilbenes and their gut microbiota metabolites in colon cancer cells: Astructure– activity relationship study. *Int. J. Mol. Sci.* **2022**, *23*, 15102. [CrossRef] [PubMed]
105. Zhang, X.; Yang, Y.; Wu, Z.; Weng, P. The modulatory effect of anthocyanins from purple sweet potato on human intestinal microbiota in vitro. *J. Agric. Food Chem.* **2016**, *64*, 2582–2590. [CrossRef]
106. Godos, J.; Micek, A.; Caruso, G.; Carota, G.; Di Mauro, A.; Furnari, F.; Di Giorgio, J.; D'Agostino, M.; Leonardi, A.; Balzano, R.M. Anthocyanin metabolites from gut microbiota and cognitive health. *J. Berry Res.* **2025**, *15*, 239–248. [CrossRef]
107. Mezhibovsky, E.; Wu, Y.; Bawagan, F.G.; Tveter, K.M.; Szeto, S.; Roopchand, D. Impact of grape polyphenols on *Akkermansia muciniphila* and the gut barrier. *AIMS Microbiol.* **2022**, *8*, 544. [CrossRef]
108. Martinovic, J.; Ambrus, R.; Planinic, M.; Selo, G.; Klaric, A.-M.; Perkovic, G.; Bucic-Kojic, A. Microencapsulation of grape pomace extracts with alginate-based coatings by freeze-drying: Release kinetics and in vitro bioaccessibility assessment of phenolic compounds. *Gels* **2024**, *10*, 353. [CrossRef]
109. Lamothe, S.; Azimy, N.; Bazinet, L.; Couillard, C.; Britten, M. Interaction of green tea polyphenols with dairy matrices in a simulated gastrointestinal environment. *Food Funct.* **2014**, *5*, 2621–2631. [CrossRef]
110. Mulet-Cabero, A.-I.; Torres-Gonzalez, M.; Geurts, J.; Rosales, A.; Farhang, B.; Marmonier, C.; Ulleberg, E.K.; Hocking, E.; Neiderer, I.; Gandolfi, I. The dairy matrix: Its importance, definition, and current application in the context of nutrition and health. *Nutrients* **2024**, *16*, 2908. [CrossRef]
111. Dobani, S.; Pourshahidi, L.K.; Ternan, N.G.; McDougall, G.J.; Pereira-Caro, G.; Bresciani, L.; Mena, P.; Almutairi, T.M.; Crozier, A.; Tuohy, K.M. A review on the effects of flavan-3-ols, their metabolites, and their dietary sources on gut barrier integrity. *Food Funct.* **2025**, *16*, 815–830. [CrossRef]
112. Nazzaro, F.; Ombra, M.N.; Coppola, F.; De Giulio, B.; d'Acierno, A.; Coppola, R.; Fratianni, F. Antibacterial Activity and Prebiotic Properties of Six Types of Lamiaceae Honey. *Antibiotics* **2024**, *13*, 868. [CrossRef] [PubMed]
113. Coppola, F.; Abdalrazeq, M.; Fratianni, F.; Ombra, M.N.; Testa, B.; Zengin, G.; Ayala Zavala, J.F.; Nazzaro, F. Rosaceae honey: Antimicrobial activity and prebiotic properties. *Antibiotics* **2025**, *14*, 298. [CrossRef] [PubMed]
114. Snoussi, M.; Noumi, E.; Hajlaoui, H.; Bouslama, L.; Hamdi, A.; Saeed, M.; Alreshidi, M.; Adnan, M.; Al-Rashidi, A.; Aouadi, K.; et al. Phytochemical Profiling of *Allium subhirsutum* L. Aqueous Extract with Antioxidant, Antimicrobial, Antibiofilm, and Anti-Quorum Sensing Properties: In Vitro and In Silico Studies. *Plants* **2021**, *11*, 495. [CrossRef]
115. Gibson, G.R.; Hutkins, R.; Sanders, M.E.; Prescott, S.L.; Reimer, R.A.; Salminen, S.J.; Scott, K.; Stanton, C.; Swanson, K.S.; Cani, P.D. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. *Nat. Rev. Gastr. Hepat.* **2017**, *14*, 491–502. [CrossRef] [PubMed]
116. Perez-Burillo, S.; Navajas-Porras, B.; Lopez-Maldonado, A.; Hinojosa-Nogueira, D.; Pastoriza, S.; Rufian-Henares, J.A. Green tea and its relation to human gut microbiome. *Molecules* **2021**, *26*, 3907. [CrossRef]
117. WHO. Antimicrobial Resistance. 2025. Available online: https://www.who.int/news-room/fact-sheets/detail/antimicrobial-resistance (accessed on 25 September 2025).
118. Helmy, Y.A.; Taha-Abdelaziz, K.; Hawwas, H.A.E.H.; Ghosh, S.; AlKafaas, S.S.; Moawad, M.M.; Saied, E.M.; Kassem, I.I.; Mawad, A.M. Antimicrobial Resistance and Recent Alternatives to Antibiotics for the Control of Bacterial Pathogens with an Emphasis on Foodborne Pathogens. *Antibiotics* **2023**, *12*, 274. [CrossRef]
119. Friedman, N.D.; Temkin, E.; Carmeli, Y. The negative impact of antibiotic resistance. *Clin. Microbiol. Infect.* **2016**, *22*, 416–422. [CrossRef] [PubMed]
120. Hailu, W.; Helmy, Y.A.; Carney-Knisely, G.; Kauffman, M.; Fraga, D.; Rajashekara, G. Prevalence and Antimicrobial Resistance Profiles of Foodborne Pathogens Isolated from Dairy Cattle and Poultry Manure Amended Farms in Northeastern Ohio, the United States. *Antibiotics* **2021**, *10*, 1450. [CrossRef]
121. FDA. *Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals*; Department of Health and Human Services: Washington, DC, USA, 2011.
122. Murray, C.J.; Ikuta, K.S.; Sharara, F.; Swetschinski, L.; Aguilar, G.R.; Gray, A.; Han, C.; Bisignano, C.; Rao, P.; Wool, E.; et al. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *Lancet* **2022**, *399*, 629–655. [CrossRef]
123. Scharff, R.L. Food Attribution and Economic Cost Estimates for Meat- and Poultry-Related Illnesses. *J. Food Prot.* **2020**, *83*, 959–967. [CrossRef]
124. Bhunia, A.K. Introduction to foodborne pathogens. In *Foodborne Microbial Pathogens: Mechanisms and Pathogenesis*; Springer: New York, NY, USA, 2018; pp. 1–23.
125. Coppola, F.; Fratianni, F.; Bianco, V.; Wang, Z.; Pellegrini, M.; Coppola, R.; Nazzaro, F. New Methodologies as Opportunities in the Study of Bacterial Biofilms, Including Food-Related Applications. *Microorganisms* **2025**, *13*, 1062. [CrossRef] [PubMed]
126. Flemming, H.-C.; Wingender, J.; Szewzyk, U.; Steinberg, P.; Rice, S.A.; Kjelleberg, S. Biofilms: An emergent form of bacterial life. *Nat. Rev. Microbiol.* **2016**, *14*, 563–575. [CrossRef]

127. Friedman, M. Antibacterial, antiviral, and antifungal properties of wines and winery byproducts in relation to their flavonoid content. *J. Agric. Food Chem.* **2014**, *62*, 6025–6042. [CrossRef]
128. Daglia, M. Polyphenols as antimicrobial agents. *Curr. Opin. Biotechnol.* **2012**, *23*, 174–181. [CrossRef]
129. Mandal, M.K.; Domb, A.J. Antimicrobial activities of natural bioactive polyphenols. *Pharmaceutics* **2024**, *16*, 718. [CrossRef]
130. Hussain, Y.; Alam, W.; Ullah, H.; Dacrema, M.; Daglia, M.; Khan, H.; Arciola, C.R. Antimicrobial potential of curcumin: Therapeutic potential and challenges to clinical applications. *Antibiotics* **2022**, *11*, 322. [CrossRef]
131. Friedman, M. Overview of antibacterial, antitoxin, antiviral, and antifungal activities of tea flavonoids and teas. *Mol. Nutr. Food Res.* **2007**, *51*, 116–134. [CrossRef]
132. Lima, V.N.; Oliveira-Tintino, C.D.; Santos, E.S.; Morais, L.P.; Tintino, S.R.; Freitas, T.S.; Geraldo, Y.S.; Pereira, R.L.; Cruz, R.P.; Menezes, I.R. Antimicrobial and enhancement of the antibiotic activity by phenolic compounds: Gallic acid, caffeic acid and pyrogallol. *Microbial Pathog.* **2016**, *99*, 56–61. [CrossRef]
133. Wu, M.; Luo, Q.; Nie, R.; Yang, X.; Tang, Z.; Chen, H. Potential implications of polyphenols on aging considering oxidative stress, inflammation, autophagy, and gut microbiota. *Cri. Rev. Food Sci. Nutr.* **2021**, *61*, 2175–2193. [CrossRef] [PubMed]
134. Gimenez-Bastida, J.; Truchado, P.; Larrosa, M.; Espin, J.; Tomas-Barberán, F.; Allende, A.; Garcia-Conesa, M.T. Urolithins, ellagitannin metabolites produced by colon microbiota, inhibit quorum sensing in *Yersinia enterocolitica*: Phenotypic response and associated molecular changes. *Food Chem.* **2012**, *132*, 1465–1474. [CrossRef] [PubMed]
135. Taiswa, A.; Andriolo, J.M.; Hailer, M.K.; Skinner, J.L. Electrospun controlled release anti-quorum sensing filter for biofouling prevention in MCE membranes. *Separ. Purif. Technol.* **2024**, *332*, 125874. [CrossRef]
136. Fan, Y.; Pedersen, O. Gut microbiota in human metabolic health and disease. *Nat. Rev. Microbiol.* **2021**, *19*, 55–71. [CrossRef]
137. Zhang, Y.-M.; Rock, C.O. Evaluation of epigallocatechin gallate and related plant polyphenols as inhibitors of the FabG and FabI reductases of bacterial type II fatty-acid synthase. *J. Biol. Chem.* **2004**, *279*, 30994–31001. [CrossRef] [PubMed]
138. Gorniak, I.; Bartoszewski, R.; Króliczewski, J. Comprehensive review of antimicrobial activities of plant flavonoids. *Phytochem. Rev.* **2019**, *18*, 241–272. [CrossRef]
139. Karas, D.; Ulrichova, J.; Valentova, K. Galloylation of polyphenols alters their biological activity. *Food Chem. Toxicol.* **2017**, *105*, 223–240. [CrossRef]
140. Wang, R.; Peng, J.; Shi, X.; Cao, S.; Xu, Y.; Xiao, G.; Li, C. Change in membrane fluidity induced by polyphenols is highly dependent on the position and number of galloyl groups. *Biochim. Biophys. Acta Biomembr.* **2022**, *1864*, 184015. [CrossRef]
141. Wang, Q.; Cao, J.; Yu, H.; Zhang, J.; Yuan, Y.; Shen, X.; Li, C. The effects of EGCG on the mechanical, bioactivities, cross-linking and release properties of gelatin film. *Food Chem.* **2019**, *271*, 204–210. [CrossRef] [PubMed]
142. Cui, Y.; Oh, Y.; Lim, J.; Youn, M.; Lee, I.; Pak, H.; Park, W.; Jo, W.; Park, S. AFM study of the differential inhibitory effects of the green tea polyphenol (−)-epigallocatechin-3-gallate (EGCG) against Gram-positive and Gram-negative bacteria. *Food Microbiol.* **2012**, *29*, 80–87. [CrossRef] [PubMed]
143. Matilla-Cuenca, L.; Toledo-Arana, A.; Valle, J. Anti-biofilm molecules targeting functional amyloids. *Antibiotics* **2021**, *10*, 795. [CrossRef]
144. Matilla-Cuenca, L.; Gil, C.; Cuesta, S.; Rapun-Araiz, B.; Ziemyte, M.; Mira, A.; Lasa, I.; Valle, J. Antibiofilm activity of flavonoids on staphylococcal biofilms through targeting BAP amyloids. *Sci. Rep.* **2020**, *10*, 18968. [CrossRef] [PubMed]
145. Slobodnikova, L.; Fialova, S.; Rendekova, K.; Kovac, J.; Mucaji, P. Antibiofilm activity of plant polyphenols. *Molecules* **2016**, *21*, 1717. [CrossRef]
146. Sonnleitner, D.; Sommer, C.; Scheibel, T.; Lang, G. Approaches to inhibit biofilm formation applying natural and artificial silk-based materials. *Mat. Sci. Eng. C* **2021**, *131*, 112458. [CrossRef]
147. Nassarawa, S.S.; Nayik, G.A.; Gupta, S.D.; Areche, F.O.; Jagdale, Y.D.; Ansari, M.J.; Hemeg, H.A.; Al-Farga, A.; Alotaibi, S.S. Chemical aspects of polyphenol-protein interactions and their antibacterial activity. *Crit. Rev. Food Sci. Nutr.* **2023**, *63*, 9482–9505. [CrossRef]
148. De Rossi, L.; Rocchetti, G.; Lucini, L.; Rebecchi, A. Antimicrobial potential of polyphenols: Mechanisms of action and microbial responses— A narrative review. *Antioxidants* **2025**, *14*, 200. [CrossRef] [PubMed]
149. Wang, Y.; Lam, A.T. Epigallocatechin gallate and gallic acid affect colonization of abiotic surfaces by oral bacteria. *Arch. Oral Biol.* **2020**, *120*, 104922. [CrossRef]
150. Trentin, D.S.; Silva, D.B.; Frasson, A.P.; Rzhepishevska, O.; da Silva, M.V.; de, L.; Pulcini, E.; James, G.; Soares, G.V.; Tasca, T.; et al. Natural green coating inhibits adhesion of clinically important bacteria. *Sci. Rep.* **2015**, *5*, 8287. [CrossRef]
151. Chen, X.; Sun, M.; Zhang, L.; Hu, Y.; Yang, Z.; Duan, S.; Xu, F.-J.; Jing, J. A one-step polyphenol-based functionalization strategy of dual-enhanced antibacterial and osteogenic surfaces. *Chem. Engin. J.* **2024**, *490*, 151792. [CrossRef]
152. Bae, J.-Y.; Seo, Y.-H.; Oh, S.-W. Antibacterial activities of polyphenols against foodborne pathogens and their application as antibacterial agents. *Food Sci. Biotechnol.* **2022**, *31*, 985–997. [CrossRef]
153. Woolard, K.J. *Synthesis and Derivatization of Compounds for the Treatment of Salmonella enterica Infections*; University of Notre Dame: Notre Dame, IN, USA, 2023.

154. Lostroh, C.P.; Lee, C.A. The *Salmonella* pathogenicity island-1 type III secretion system. *Microbes Infect.* **2001**, *3*, 1281–1291. [CrossRef]
155. Cheng, G.; Jian, S.; Li, W.; Yan, L.; Chen, T.; Cheng, T.; Liu, Z.; Ye, G.; Tang, H.; Zhang, L. Epigallocatechin gallate protects mice from *Salmonella enterica* ser. Typhimurium infection by modulating bacterial virulence through quorum sensing inhibition. *Front. Cell. Infect. Microbiol.* **2024**, *14*, 1432111. [CrossRef]
156. Wong, H.S.; Maker, G.L.; Trengove, R.D.; O' Handley, R.M. Gas chromatography-mass spectrometry-based metabolite profiling of *Salmonella enterica* serovar Typhimurium differentiates between biofilm and planktonic phenotypes. *Appl. Environm. Microbiol.* **2015**, *81*, 2660–2666. [CrossRef]
157. Hamilton, S.; Bongaerts, R.J.; Mulholland, F.; Cochrane, B.; Porter, J.; Lucchini, S.; Lappin-Scott, H.M.; Hinton, J.C. The transcriptional programme of *Salmonella enterica* serovar Typhimurium reveals a key role for tryptophan metabolism in biofilms. *Bmc Genomics* **2009**, *10*, 599. [CrossRef] [PubMed]
158. MacKenzie, K.D.; Palmer, M.B.; Köster, W.L.; White, A.P. Examining the link between biofilm formation and the ability of pathogenic *Salmonella* strains to colonize multiple host species. *Front. Veterin. Sci.* **2017**, *4*, 138. [CrossRef] [PubMed]
159. Polat, G. Natural Compounds with Antibacterial Activity Against *Cronobacter* spp. in Powdered Infant. *Nat. Compounds Food Safety Preserv.* **2021**, *20*, 59596418. [CrossRef]
160. Guan, N.; Shi, Y.; Tong, H.; Yang, Y.; Li, J.; Guo, D.; Wang, X.; Shan, Z.; Lu, X.; Shi, C. Inhibition of *Cronobacter sakazakii* biofilm formation and expression of virulence factors by coenzyme Q0. *Foodborne Pathog. Dis.* **2023**, *20*, 442–452. [CrossRef]
161. Tian, L.; Wu, M.; Guo, W.; Li, H.; Gai, Z.; Gong, G. Evaluation of the membrane damage mechanism of chlorogenic acid against *Yersinia enterocolitica* and *Enterobacter sakazakii* and its application in the preservation of raw pork and skim milk. *Molecules* **2021**, *26*, 6748. [CrossRef] [PubMed]
162. Vazquez-Armenta, F.J.; Alvarez-Armenta, A.; Sugich-Miranda, R.; Ayala-Zavala, F.; Morales-Ortega, A.; Arvizu-Flores, A.A.; Lopez-Zavala, A.A. Inhibition mechanism of lecithin-dependent hemolysin from *Vibrio parahaemolyticus* by flavonoids: An enzyme kinetic and structural approach. *Catalysts* **2025**, *15*, 257. [CrossRef]
163. Faleye, O.S.; Lee, J.-H.; Lee, J. Selected flavonoids exhibit antibiofilm and antibacterial effects against *Vibrio* by disrupting membrane integrity, virulence and metabolic activities. *Biofilm* **2023**, *6*, 100165. [CrossRef] [PubMed]
164. She, W.; Cheng, A.; Ye, W.; Zeng, P.; Wang, H.; Qian, P.-Y. Mode of action of antimicrobial agents albofungins in eradicating penicillin-and cephalosporin-resistant *Vibrio parahaemolyticus* biofilm. *Microbiol. Spectr.* **2023**, *11*, e01563-23. [CrossRef]
165. Ali, I.A.; Neelakantan, P. Antibiofilm activity of phytochemicals against *Enterococcus faecalis*: A literature review. *Phytother. Res.* **2022**, *36*, 2824–2838. [CrossRef]
166. Vazquez-Boland, J.A.; Kuhn, M.; Berche, P.; Chakraborty, T.; Dominguez-Bernal, G.; Goebel, W.; González-Zorn, B.; Wehland, J.; Kreft, J. *Listeria pathogenesis* and molecular virulence determinants. *Clin. Microbiol. Rev.* **2001**, *14*, 584–640. [CrossRef]
167. Du, W.; Zhou, M.; Liu, Z.; Chen, Y.; Li, R. Inhibition effects of low concentrations of epigallocatechin gallate on the biofilm formation and hemolytic activity of *Listeria monocytogenes*. *Food Control* **2018**, *85*, 119–126. [CrossRef]
168. Santos, C.A.; Lima, E.M.F.; Franco, B.D.G.d.M.; Pinto, U.M. Exploring phenolic compounds as quorum sensing inhibitors in foodborne bacteria. *Front. Microbiol.* **2021**, *12*, 735931. [CrossRef]
169. Vazquez-Armenta, F.; Hernandez-Oñate, M.; Martinez-Tellez, M.; Lopez-Zavala, A.; Gonzalez-Aguilar, G.; Gutierrez-Pacheco, M.; Ayala-Zavala, J. Quercetin repressed the stress response factor (*sigB*) and virulence genes (*prfA*, *actA*, *inlA*, and *inlC*), lower the adhesion, and biofilm development of *L. monocytogenes*. *Food Microbiol.* **2020**, *87*, 103377. [CrossRef]
170. Borges, A.; Saavedra, M.J.; Simoes, M. Insights on antimicrobial resistance, biofilms and the use of phytochemicals as new antimicrobial agents. *Curr. Med. Chem.* **2015**, *22*, 2590–2614. [CrossRef]
171. Snoussi, M.; Lajimi, R.H.; Latif, S.; Hamadou, W.S.; Alreshidi, M.; Ashraf, S.A.; Patel, M.; Humaidi, J.R.; Anouar, E.H.; Kadri, A.; et al. Green synthesis and characterization of silver nanoparticles from *Ducrosia flabellifolia* Boiss. aqueous extract: Anti-quorum sensing screening and antimicrobial activities against ESKAPE pathogens. *Cell. Mol. Biol.* **2024**, *70*, 88–96. [CrossRef]
172. Terzic, M.; Zengin, G.; Mocan, A.; Frumuzachi, O.; Cetiz, M.V.; Caprioli, G.; Acquaticci, L.; Angeloni, S.; Senkardes, I.; Saka, E. Connecting chemical and biological properties to identify new functional materials: A study on *Trifolium nigrescens* extracts. *Ind. Crops Prod.* **2025**, *233*, 121484. [CrossRef]
173. Deryabin, D.; Galadzhieva, A.; Kosyan, D.; Duskaev, G. Plant-derived inhibitors of AHL-mediated quorum sensing in bacteria: Modes of action. *Int. J. Mol. Sci.* **2019**, *20*, 5588. [CrossRef]
174. Truchado, P.; Larrosa, M.; Castro-Ibanez, I.; Allende, A. Plant food extracts and phytochemicals: Their role as quorum sensing inhibitors. *Trends Food Sci. Technol.* **2015**, *43*, 189–204. [CrossRef]
175. de Llano, D.G.; Esteban-Fernández, A.; Sanchez-Patan, F.; Martín-Alvarez, P.J.; Moreno-Arribas, M.V.; Bartolomé, B. Anti-adhesive activity of cranberry phenolic compounds and their microbial-derived metabolites against uropathogenic *Escherichia coli* in bladder epithelial cell cultures. *Int. J. Mol. Sci.* **2015**, *16*, 12119–12130. [CrossRef]
176. Zhang, J.; Wang, D.; Sun, J.; Sun, Z.; Liu, F.; Du, L.; Wang, D. Synergistic antibiofilm effects of ultrasound and phenyllactic acid against *Staphylococcus aureus* and *Salmonella enteritidis*. *Foods* **2021**, *10*, 2171. [CrossRef] [PubMed]

177. Alakomi, H.-L.; Puupponen-Pimiä, R.; Aura, A.-M.; Helander, I.M.; Nohynek, L.; Oksman-Caldentey, K.-M.; Saarela, M. Weakening of *Salmonella* with selected microbial metabolites of berry-derived phenolic compounds and organic acids. *J. Agric. Food Chem.* **2007**, *55*, 3905–3912. [CrossRef] [PubMed]
178. Ballén, V.; Cepas, V.; Ratia, C.; Gabasa, Y.; Soto, S.M. Clinical *Escherichia coli*: From biofilm formation to new antibiofilm strategies. *Microorganisms* **2022**, *10*, 1103. [CrossRef]
179. Ramata-Stunda, A.; Petriņa, Z.; Valkovska, V.; Borodušķis, M.; Gibnere, L.; Gurkovska, E.; Nikolajeva, V. Synergistic effect of polyphenol-rich complex of plant and green propolis extracts with antibiotics against respiratory infections causing bacteria. *Antibiotics* **2022**, *11*, 160. [CrossRef]
180. Uddin Mahamud, A.S.; Nahar, S.; Ashrafudoulla, M.; Park, S.H.; Ha, S.-D. Insights into antibiofilm mechanisms of phytochemicals: Prospects in the food industry. *Crit. Rev. Food Sci. Nutr.* **2024**, *64*, 1736–1763. [CrossRef] [PubMed]
181. Bhardwaj, D.; Tiwari, D.; Upadhye, V.J.; Ramniwas, S.; Rautela, I.; Ballal, S.; Kumar, S.; Bhat, M.; Sharma, S.; Kumar, M.R. Discovery of new natural phytocompounds: The modern tools to fight against traditional bacterial pathogens. *Curr. Pharm. Biotechnol.* **2024**. [CrossRef]
182. Chen, L.; Yu, K.; Chen, L.; Zheng, X.; Huang, N.; Lin, Y.; Jia, H.; Liao, W.; Cao, J.; Zhou, T. Synergistic activity and biofilm formation effect of colistin combined with PFK-158 against colistin-resistant gram-negative bacteria. *Infect. Drug. Resist.* **2021**, *14*, 2143–2154. [CrossRef]
183. Colletti, A.; Sangiorgio, L.; Martelli, A.; Testai, L.; Cicero, A.F.; Cravotto, G. Highly active cranberry's polyphenolic fraction: New advances in processing and clinical applications. *Nutrients* **2021**, *13*, 2546. [CrossRef]
184. Tomas-Barberan, F.A.; Gonzalez-Sarrias, A.; Garcia-Villalba, R.; Nunez-Sanchez, M.A.; Selma, M.V.; Garcia-Conesa, M.T.; Espin, J.C. Urolithins, the rescue of "old" metabolites to understand a "new" concept: Metabotypes as a nexus among phenolic metabolism, microbiota dysbiosis, and host health status. *Mol. Nutr. Food Res.* **2017**, *61*, 1500901. [CrossRef] [PubMed]
185. Ghosh, S.; Erickson, D.; Chua, M.J.; Collins, J.; Jala, V.R. The microbial metabolite urolithin A reduces *Clostridioides difficile* toxin expression and toxin-induced epithelial damage. *Msystems* **2024**, *9*, e01255-23. [CrossRef]
186. Nandi, P.; Kanthal, J.; Hansda, S.; Ghosh, S. Neurophysiological Implications of Food Safety: Food Born Pathogens and Its Neurological Impact. In *Physiological Perspectives on Food Safety: Exploring the Intersection of Health and Nutrition*; Sarkar, T., Hamad, A., Chatterjee, A., Eds.; Springer: Cham, Switzerland, 2025. [CrossRef]
187. Marano, G.; Mazza, M.; Lisci, F.M.; Ciliberto, M.; Traversi, G.; Kotzalidis, G.D.; Berardis, D.D.; Laterza, L.; Sani, G.; Gasbarrini, A.; et al. The microbiota–gut–brain- axis: Psychoneuroimmunological insights. *Nutrients* **2023**, *15*, 1496. [CrossRef]
188. Mhanna, A.; Martini, N.; Hmaydoosh, G.; Hamwi, G.; Jarjanazi, M.; Zaifah, G.; Kazzazo, R.; Mohamad, A.H.; Alshehabi, Z. The correlation between gut microbiota and both neurotransmitters and mental disorders: A narrative review. *Medicine* **2024**, *103*, e37114. [CrossRef] [PubMed]
189. Aljeradat, B.; Kumar, D.; Abdulmuizz, S.; Kundu, M.; Almealawy, Y.F.; Batarseh, D.R.; Atallah, O.; Ennabe, M.; Alsarafandi, M.; Alan, A.; et al. Neuromodulation and the gut–brain-axis: Therapeutic mechanisms and implications for gastrointestinal and neurological disorders. *Pathophysiology* **2024**, *31*, 244–268. [CrossRef]
190. Chaudhry, T.S.; Senapati, S.G.; Gadam, S.; Mannam, H.P.S.S.; Voruganti, H.V.; Abbasi, Z.; Abhinav, T.; Challa, A.B.; Pallipamu, N.; Bheemisetty, N.; et al. The impact of microbiota on the gut–brain-axis: Examining the complex interplay and implications. *J. Clin. Med.* **2023**, *12*, 5231. [CrossRef]
191. Bhatt, A.P.; Redinbo, M.R.; Bultman, S.J. The role of the microbiome in cancer development and therapy. *CA A Cancer J. Clin.* **2017**, *67*, 326–344. [CrossRef] [PubMed]
192. Hamon, M.A.; Cossart, P. Histone modifications and chromatin remodeling during bacterial infections. *Cell Host Micr.* **2008**, *4*, 100–109. [CrossRef]
193. Warren, A.; Nyavor, Y.; Zarabian, N.; Mahoney, A.; Frame, L.A. The microbiota-gut-brain-immune interface in the pathogenesis of neuroinflammatory diseases: A narrative review of the emerging literature. *Front. Immunol.* **2024**, *15*, 1365673. [CrossRef] [PubMed]
194. Nakhal, M.M.; Yassin, L.K.; Alyaqoubi, R.; Saeed, S.; Alderei, A.; Alhammadi, A.; Alshehhi, M.; Almehairbi, A.; Al Houqani, S.; BaniYas, S.; et al. The microbiota–gut–brain-axis and neurological disorders: A comprehensive review. *Life* **2024**, *14*, 1234. [CrossRef]
195. Shu, Z.; Dan, D.; Ming, X.; Wei, C.; Huan, D. Direct and indirect effects of pathogenic bacteria on the integrity of intestinal barrier. *Therapeutic Adv. Gastroenterol.* **2023**, *16*, 17562848231176427. [CrossRef]
196. Camilleri, M. Leaky gut: Mechanisms, measurement and clinical implications in humans. *Gut* **2019**, *68*, 1516–1526. [CrossRef]
197. Haroon, E.; Miller, A.H.; Sanacora, G. Inflammation, glutamate, and glia: A trio of trouble in mood disorders. *Neuropsychopharmacology* **2017**, *42*, 193–215. [CrossRef]
198. Boyd, R.J.; Avramopoulos, D.; Jantzie, L.L.; McCallion, A.S. Neuroinflammation represents a common theme amongst genetic and environmental risk factors for Alzheimer and Parkinson diseases. *J. Neuroinflammation* **2022**, *19*, 223. [CrossRef] [PubMed]
199. Disson, O.; Lecuit, M. Targeting of the central nervous system by *Listeria monocytogenes*. *Virulence* **2012**, *3*, 213–221. [CrossRef]

200. Taha, A.R. Central nervous system infection. In *Highly Infectious Diseases in Critical Care: A Comprehensive Clinical Guide*; Springer International Publishing: Cham, Switzerland, 2020; pp. 147–174.
201. Liu, D. Clostridium botulinum and associated neurotoxins. In *Molecular Medical Microbiology*; Academic Press: Cambridge, MA, USA, 2024; pp. 933–944. [CrossRef]
202. Zhan, C.Y. *E.coli* pathogenesis: From commensal to pathogenic strains. *Mol. Microbiol. Res.* **2025**, *15*, 18–27.
203. Goldstein, J.; Nuñez-Goluboay, K.; Pinto, A. Therapeutic strategies to protect the central nervous system against Shiga toxin from enterohemorrhagic *Escherichia coli*. *Curr. Neuropharmacol.* **2021**, *19*, 24–44. [CrossRef] [PubMed]
204. Jiang, T.; Zhu, K.; Kang, G.; Wu, G.; Tan, Y. Neuroinflammation in neurodegenerative disorders: Activation of microglia by microbial infection. *AIMS Molecular Science* **2025**, *12*, 198–215. [CrossRef]
205. De Chiara, S.; De Simone Carone, L.; Cirella, R.; Andretta, E.; Silipo, A.; Molinaro, A.; Mercogliano, M.; Di Lorenzo, F. Beyond the toll-like receptor 4. Structure-dependent lipopolysaccharide recognition systems: How far are we? *Chem. Med. Chem.* **2025**, *20*, e202400780. [CrossRef]
206. Li, L.; Acioglu, C.; Heary, R.F.; Elkabes, S. Role of astroglial toll-like receptors (TLRs) in central nervous system infections, injury and neurodegenerative diseases. *Brain Behav. Immun.* **2021**, *91*, 740–755.
207. Cassidy, B.R.; Zhang, M.; Drevets, D.A. Neuroimmune Consequences of L. monocytogenes Infection. In *In Vitro and In Vivo Models to Study Infections of the Central Nervous System*; Iovino, F., Ed.; Humana: New York, NY, USA, 2025; pp. 35–49. [CrossRef]
208. Monash, A.; Tam, J.; Rosen, O.; Soreq, H. Botulinum neurotoxins: History, mechanism, and applications. A narrative review. *J. Neurochem.* **2025**, *169*, e70187. [CrossRef]
209. Trisal, A.; Singh, I.; Garg, G.; Jorwal, K.; Singh, A.K. Gut–brain-axis and brain health: Modulating neuroinflammation, cognitive decline, and neurodegeneration. *3 Biotech* **2025**, *15*, 25. [CrossRef] [PubMed]
210. Gouri, H.; Bhalla, G. Neurotoxic chemistry: Unraveling the chemical mechanisms connecting environmental toxin exposure to neurological disorders. *J. Integr. Sci. Technol.* **2025**, *13*, 1064. [CrossRef]
211. Rajasekaran, R.; Saahithya, R. *Elements of Reproduction and Reproductive Diseases of Goats*; Tanmoy, R., Ed.; Wiley online: Hoboken, NJ, USA, 2025; pp. 463–472.
212. Clauss, H.E.; Lorber, B. Central nervous system infection with *Listeria monocytogenes*. *Curr. Infect. Dis. Rep.* **2008**, *10*, 300–306. [CrossRef]
213. Lee, M.S.; Tesh, V.L. Roles of Shiga toxins in immunopathology. *Toxins* **2019**, *11*, 212. [CrossRef]
214. Vida, C.; Gonzalez, M.E.; De la Fuente, M. Increase of oxidation and inflammation in nervous and immune systems with aging and anxiety. *Curr. Pharm. Des.* **2014**, *20*, 4656–4678. [CrossRef] [PubMed]
215. Abdol Samat, H.N.; Razali, N.N.; Mahadzir, H.; Tengku Muhammad, T.S.; Ling, K.H.; Mansor, N.I.; Abidin, S.Z. The Interplay of Inflammation and Gut-Microbiota Dysbiosis in Alzheimer's Disease: Mechanisms and Therapeutic Potential. *Int. J. Mol. Sci.* **2025**, *26*, 8905. [CrossRef]
216. Yang, K.; Chen, J.; Wang, T.; Zhang, Y. Pathogenesis of sepsis-associated encephalopathy: More than blood–brain barrier dysfunction. *Mol. Biol. Rep.* **2022**, *49*, 10091–10099. [CrossRef] [PubMed]
217. Tran, V.T.A.; Zhu, X.; Jamsranjav, A.; Lee, L.P.; Cho, H. *Escherichia coli* K1-colibactin meningitis induces microglial NLRP3/IL-18 exacerbating H3K4me3-synucleinopathy in human inflammatory gut-brain-axis. *Commun. Biol.* **2025**, *8*, 382. [CrossRef]
218. Muenkel, M.; Keskin, E.; Balmes, A.; Schäffer, T.E.; Romer, F.; Lebtig, M.; Kretschmer, D.; Wright, K.; Loskill, P.; Mostowy, S.; et al. *Listeria-Infected Macrophages Promote Biomechanical Alterations in Endothelial Cell Monolayers for Transmigration*; Cell Press: Cambridge, MA, USA, 2025.
219. Wortel, I.M.; Kim, S.; Liu, A.Y.; Ibarra, E.C.; Miller, M.J. *Listeria* motility increases the efficiency of epithelial invasion during intestinal infection. *PLoS Pathogens* **2022**, *18*, e1011028.
220. Quan, Y.; Wang, Y.; Gao, S.; Yuan, S.; Song, S.; Liu, B.; Wang, Y. Breaking the fortress: A mechanistic review of meningitis-causing bacteria breaching tactics in blood brain barrier. *Cell Commun. Signal.* **2025**, *23*, 235. [CrossRef] [PubMed]
221. Li, H.; Liu, C.C.; Zheng, H.; Huang, T.Y. Amyloid, tau, pathogen infection and antimicrobial protection in Alzheimer's disease–conformist, nonconformist, and realistic prospects for AD pathogenesis. *Transl. Neurod.* **2018**, *7*, 34.
222. Blake, S.; Harding, T.; Baroni, L.; Harding, M.; Blake, C.; Piboolnurak, P.; Grant, W. Reducing dietary lipopolysaccharides to slow progression of cognitive impairment and Alzheimer's disease. *J. Brain Sci.* **2024**, *7*, 10–18488. [CrossRef]
223. Brown, G.C.; Camacho, M.; Williams-Gray, C.H. The endotoxin hypothesis of Parkinson 's disease. *Mov. Dis.* **2023**, *38*, 1143–1155. [CrossRef]
224. Brooks, P.T.; Brakel, K.A.; Bell, J.A.; Bejcek, C.E.; Gilpin, T.; Brudvig, J.M.; Mansfield, L.S. Transplanted human fecal microbiota enhanced Guillain Barré syndrome autoantibody responses after *Campylobacter jejuni* infection in C57BL/6 mice. *Microbiome* **2017**, *5*, 92. [CrossRef]
225. Hansda, S.; Das, H. Unraveling the Bone–Brain Communication Network. *Biology* **2025**, *14*, 1279. [CrossRef] [PubMed]
226. Sweeney, M.D.; Zhao, Z.; Montagne, A.; Nelson, A.R.; Zlokovic, B.V. Blood-brain barrier: From physiology to disease and back. *Physiol. Rev.* **2018**, *99*, 21–78. [CrossRef] [PubMed]

227. Van De Haar, H.J.; Burgmans, S.; Jansen, J.F.; Van Osch, M.J.; Van Buchem, M.A.; Muller, M.; Hofman, P.A.; Verhey, F.R.; Backes, W.H. Blood-brain barrier leakage in patients with early Alzheimer disease. *Radiology* **2016**, *281*, 527–535. [CrossRef]
228. Dominguez-Lopez, I.; Lopez-Yerena, A.; Vallverdu-Queralt, A.; Pallas, M.; Lamuela-Raventos, R.M.; Perez, M. From the gut to the brain: The long journey of phenolic compounds with neurocognitive effects. *Nutr. Rev.* **2025**, *83*, e533–e546. [CrossRef]
229. Gong, Q.Y.; Cai, L.; Jing, Y.; Wang, W.; Yang, D.X.; Chen, S.W.; Tian, H.L. Urolithin A alleviates blood-brain barrier disruption and attenuates neuronal apoptosis following traumatic brain injury in mice. *Neu. Regen. Res.* **2022**, *17*, 2007–2013.
230. Cecarini, V.; Cuccioloni, M.; Zheng, Y.; Bonfili, L.; Gong, C.; Angeletti, M.; Mena, P.; Del Rio, D.; Eleuteri, A.M. Flavan-3-ol microbial metabolites modulate proteolysis in neuronal cells reducing amyloid- beta (1-42) levels. *Mol. Nutr. Food Res.* **2021**, *65*, 2100380. [CrossRef]
231. Gonzalez de Llano, D.; Roldan, M.; Parro, L.; Bartolome, B.; Moreno-Arribas, M.V. Activity of microbial-derived phenolic acids and their conjugates against LPS-induced damage in neuroblastoma cells and macrophages. *Metabolites* **2023**, *13*, 108. [CrossRef] [PubMed]
232. Ruotolo, R.; Minato, I.; La Vitola, P.; Artioli, L.; Curti, C.; Franceschi, V.; Brindani, N.; Amidani, D.; Colombo, L.; Salmona, M. Flavonoid-derived human phenyl–γ-valerolactone metabolites selectively detoxify amyloid-β oligomers and prevent memory impairment in a mouse model of Alzheimer' s disease. *Mol. Nutr. Food Res.* **2020**, *64*, 1900890. [CrossRef] [PubMed]
233. Melrose, J. The potential of flavonoids and flavonoid metabolites in the treatment of neurodegenerative pathology in disorders of cognitive decline. *Antioxidants* **2023**, *12*, 663. [CrossRef] [PubMed]
234. Holland, T.M.; Agarwal, P.; Wang, Y.; Leurgans, S.E.; Bennett, D.A.; Booth, S.L.; Morris, M.C. Dietary flavonols and risk of Alzheimer dementia. *Neurology* **2020**, *94*, e1749–e1756. [CrossRef]
235. Sekikawa, A.; Wharton, W.; Murray-Krezan, C.; Wu, M.; Chang, Y.; Snitz, B.E.; Coccari, M.; Yang, S.; Love, M.L.; Cusick, D. ACE trial design: Equol targeting estrogen receptor-β in vascular and cognitive aging. *Alzheimer's Dement.* **2025**, *1*, e70144. [CrossRef]
236. Fox, S.H.; Cardoso, F. Unmet Needs in Parkinson' s Disease. *Movem. Dis. Clin Pract.* **2023**, *10* (Suppl. S2), S47.
237. Farez, M.F.; Fiol, M.P.; Gaitán, M.I.; Quintana, F.J.; Correale, J. Sodium intake is associated with increased disease activity in multiple sclerosis. *J. Neurol. Neurosurg. Psych.* **2015**, *86*, 26–31. [CrossRef] [PubMed]
238. Iadecola, C. The pathobiology of vascular dementia. *Neuron* **2013**, *80*, 844–866. [CrossRef]
239. Valls-Pedret, C.; Sala-Vila, A.; Serra-Mir, M.; Corella, D.; de la Torre, R.; Martínez-González, M.Á.; Martínez-Lapiscina, E.H.; Fitó, M.; Pérez-Heras, A.; Salas-Salvadó, J. Mediterranean diet and age-related cognitive decline: A randomized clinical trial. *JAMA Internal Med.* **2015**, *175*, 1094–1103. [CrossRef] [PubMed]
240. Martín-Peláez, S.; Mosele, J.I.; Pizarro, N.; Farras, M.; De la Torre, R.; Subirana, I.; Pérez-Cano, F.J.; Castaner, O.; Solà, R.; Fernandez-Castillejo, S. Effect of virgin olive oil and thyme phenolic compounds on blood lipid profile: Implications of human gut microbiota. *Eur. J. Nutr.* **2017**, *56*, 119–131. [CrossRef]
241. Habtemariam, S. Anti-inflammatory therapeutic mechanisms of natural products: Insight from rosemary diterpenes, carnosic acid and carnosol. *Biomedicines* **2023**, *11*, 545. [CrossRef]
242. Kaur, D.; Singh, S. Isoquercetin neuroprotective molecular targets in Parkinson's disease: Recent highlights and future perspectives. *Lett. Drug Des. Discov.* **2024**, *21*, 3639–3647. [CrossRef]
243. Jalouli, M.; Rahman, M.A.; Biswas, P.; Rahman, H.; Harrath, A.H.; Lee, I.-S.; Kang, S.; Choi, J.; Park, M.N.; Kim, B. Targeting natural antioxidant polyphenols to protect neuroinflammation and neurodegenerative diseases: A comprehensive review. *Front. Pharmacol.* **2025**, *16*, 1492517. [CrossRef]
244. Spagnuolo, C.; Moccia, S.; Russo, G.L. Anti-inflammatory effects of flavonoids in neurodegenerative disorders. *Eur. J. Med. Chem.* **2018**, *153*, 105–115. [CrossRef]
245. Bucciantini, M.; Leri, M.; Nardiello, P.; Casamenti, F.; Stefani, M. Olive polyphenols: Antioxidant and anti-inflammatory properties. *Antioxidants* **2021**, *10*, 1044. [CrossRef]
246. Andreux, P.A.; Blanco-Bose, W.; Ryu, D.; Burdet, F.; Ibberson, M.; Aebischer, P.; Auwerx, J.; Singh, A.; Rinsch, C. The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans. *Nature Metab.* **2019**, *1*, 595–603. [CrossRef]
247. Ju, T.; Zhang, Y.; Liu, L.; Zhao, X.; Li, X.; Liu, C.; Sun, S.; Wu, L. The role of gut microbiota–mitochondria crosstalk in neurodegeneration: Underlying mechanisms and potential therapies. *Neural Regen. Res.* **2025**, *10*, 4103. [CrossRef] [PubMed]
248. Fang, E.F.; Hou, Y.; Palikaras, K.; Adriaanse, B.A.; Kerr, J.S.; Yang, B.; Lautrup, S.; Hasan-Olive, M.M.; Caponio, D.; Dan, X. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer' s disease. *Nature neurosci.* **2019**, *22*, 401–412. [CrossRef] [PubMed]
249. Wang, Y.; Wang, K.; Yan, J.; Zhou, Q.; Wang, X. Recent progress in research on mechanisms of action of natural products against Alzheimer's disease: Dietary plant polyphenols. *Int. J. Mol. Sci.* **2022**, *23*, 13886. [CrossRef]
250. Zhong, W.; Gong, J.; Su, Q.; Farag, M.A.; Simal-Gandara, J.; Wang, H.; Cao, H. Dietary polyphenols ameliorate inflammatory bowel diseases: Advances and future perspectives to maximize their nutraceutical applications. *Phytochem. Rev.* **2025**, *24*, 1227–1259. [CrossRef]

251. Al Olayan, E.M.; Aloufi, A.S.; AlAmri, O.D.; El-Habit, O.H.; Moneim, A.E.A. Protocatechuic acid mitigates cadmium-induced neurotoxicity in rats: Role of oxidative stress, inflammation and apoptosis. *Sci. Total Environ.* **2020**, *723*, 137969. [CrossRef]
252. Gong, Z.; Huang, J.; Xu, B.; Ou, Z.; Zhang, L.; Lin, X.; Ye, X.; Kong, X.; Long, D.; Sun, X. Urolithin A attenuates memory impairment and neuroinflammation in APP/PS1 mice. *J. Neuroinflam.* **2019**, *16*, 62. [CrossRef]
253. Ray, S.K.; Mukherjee, S. Evolving interplay between dietary polyphenols and gut microbiota—an emerging importance in healthcare. *Front. Nutr.* **2021**, *8*, 634944. [CrossRef]
254. Conte, R.; Calarco, A.; Napoletano, A.; Valentino, A.; Margarucci, S.; Di Cristo, F.; Di Salle, A.; Peluso, G. Polyphenols nanoencapsulation for therapeutic applications. *J. Biomol. Res. Ther.* **2016**, *5*, 139.
255. Kim, H.J.; Li, H.; Collins, J.J.; Ingber, D.E. Contributions of microbiome and mechanical deformation to intestinal bacterial overgrowth and inflammation in a human gut-on-a-chip. *Proc. Nat. Acad. Sci. USA* **2016**, *113*, E7–E15. [CrossRef] [PubMed]

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