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Review

From Dietary Phytochemicals to Bioactive Microbial Metabolites: Biotransformation Pathways, Molecular Targets, and Translational Challenges

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Abstract

Background/Objectives: Dietary phytochemicals interact with the gut microbiota, generating metabolites with physicochemical and biological properties that may differ from those of their parent compounds. Understanding these transformations is essential for elucidating phytochemical bioactivity and evaluating potential health applications. This narrative review examines microbial biotransformation pathways, bioactive metabolites, molecular targets, and the challenges associated with translating experimental findings into human applications. **Methods**: A narrative review was developed using searches in PubMed/MEDLINE, Scopus and Web of Science and complementary reference identification, with literature coverage extending through 31 October 2026. Three reviewers independently screened 882 deduplicated records, retaining 322 for full-text assessment; disagreements were resolved by consensus. Co-authors subsequently synthesised relevant in vitro, ex vivo, animal and human evidence. Evidence was synthesised narratively using a mechanistic framework encompassing phytochemical classes, microbial transformations, metabolite formation, molecular signalling pathways, and physiological effects. **Results**: Microbial reactions, including deglycosylation, reduction, demethylation, and ring cleavage, contribute to the formation of metabolites such as urolithins, equol, enterolignans, and phenolic acid derivatives. Experimental studies indicate that selected metabolites can modulate signalling pathways involved in oxidative stress, inflammation, energy metabolism, and intestinal homeostasis, including Nrf2, NF-κB, AMPK, and AhR. However, the clinical relevance of many proposed mechanisms remains uncertain. Major translational challenges

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include incomplete pharmacokinetic characterisation, discrepancies between experimental and physiologically achievable concentrations, interindividual variability in microbial metabolism, and limited clinical validation. **Conclusions**: Microbial biotransformation is an important determinant of phytochemical metabolism and biological activity. Improved characterisation of metabolite exposure, microbial metabolic phenotypes, and human responses is needed to establish the physiological relevance and the potential health and therapeutic relevance of gut-derived phytochemical metabolites.

Keywords: dietary phytochemicals; gut microbiota; microbial biotransformation; bioactive metabolites; molecular targets; pharmacokinetics; translational research

1. Introduction

Dietary phytochemicals comprise a structurally diverse group of naturally occurring plant secondary metabolites that play important roles in plant defence against biotic and abiotic stress, pigmentation, growth regulation, and intercellular signalling [1–4]. These compounds include polyphenols, flavonoids, phenolic acids, tannins, stilbenes, lignans, terpenoids, carotenoids, glucosinolates, alkaloids, and sulfur-containing compounds, each characterised by distinct chemical structures that influence their stability, solubility, absorption, metabolism, and biological activity [1–4]. The remarkable structural diversity of dietary phytochemicals underlies their physicochemical properties and largely determines their susceptibility to microbial biotransformation, thereby shaping the formation of gut-derived metabolites and their subsequent biological activities. Epidemiological and experimental studies have associated diets rich in phytochemical-containing foods with favourable cardiometabolic and other health outcomes; however, these associations do not establish that individual phytochemicals or their metabolites directly prevent disease [5–7]. However, although phytochemical structure largely determines their physicochemical properties and metabolic fate, the biological effects of many phytochemicals cannot be explained solely by their native chemical structures or intrinsic antioxidant capacity but rather by their dynamic interactions with the gastrointestinal environment and the resident gut microbiota [1,5].

Dietary phytochemicals can undergo chemical and enzymatic transformations throughout the gastrointestinal tract, with microbial metabolism becoming particularly relevant for compounds reaching the colon. Although some low-molecular-weight compounds are readily absorbed in the small intestine, variable fractions of phytochemicals, including some polymeric polyphenols, glycosylated flavonoids, ellagitannins, and glucosinolates, may reach the colon because of their limited bioavailability, poor aqueous solubility, or resistance to digestion by human enzymes [1,8,9]. Consequently, the gut microbiota functions as an additional metabolic organ, possessing an extensive repertoire of glycosidases, esterases, hydrolases, reductases, decarboxylases, demethylases, and dehydroxylases that catalyse sequential reactions capable of profoundly modifying phytochemical structures [10–12]. These microbial transformations alter the physicochemical characteristics of phytochemicals, potentially modifying their absorption, systemic exposure, and biological activity, although these changes are compound- and metabolite-dependent [13,14].

Microbial biotransformation has therefore emerged as a fundamental determinant of phytochemical bioactivity. In addition to the potential activity of parent compounds, certain dietary phytochemicals act as substrates for microbial metabolites that may contribute to physiological responses [5,14]. Representative examples include the conversion of ellagitannins into urolithins, flavonoids into phenolic acids and valerolactones, mangiferin into norathyriol, glycosides into biologically active aglycones, and numerous aromatic com-

pounds into smaller phenolic derivatives through ring-cleavage reactions [10,13,15–17]. These metabolic conversions are highly dependent on the taxonomic composition and functional capacity of the gut microbiota, thereby contributing to the marked interindividual variability observed in the biological responses to phytochemical-rich diets [5,14]. Recent developments in metagenomics, metabolomics, transcriptomics, and integrated multi-omics approaches have substantially improved the characterisation of microbial metabolic pathways involved in phytochemical degradation and metabolite production [5,14]. These approaches have helped identify associations and experimental mechanisms linking gut-derived metabolites with pathways involved in intestinal homeostasis, epithelial barrier integrity, immune function, oxidative stress, inflammatory signalling, lipid and glucose metabolism, and host energy balance [12,18–20]. Furthermore, microbial metabolites including short-chain fatty acids, phenolic metabolites, indole derivatives, bile acid metabolites, and other microbial products act as signalling molecules capable of influencing distant organs through endocrine, metabolic, neural, and immune pathways [21–23].

Among these systemic effects, growing attention has been devoted to the microbiota–gut–brain axis, a bidirectional communication network linking intestinal microorganisms with the central nervous system. Experimental findings suggest that selected microbial metabolites may influence processes related to blood–brain barrier integrity, neurotransmitter synthesis, neuroinflammation, microglial activation, hypothalamic–pituitary–adrenal axis activity, and cognitive function [21,23–27]. Nevertheless, neurological outcomes represent only one component of the potential physiological implications of microbial phytochemical metabolism, including cardiometabolic regulation, intestinal health, immune modulation, and mechanisms relevant to cancer biology [28–30].

Although substantial progress has been made in characterising individual phytochemicals, microbial taxa, and health outcomes, current knowledge remains fragmented. Existing reviews frequently address phytochemical chemistry, gut microbiota, microbial metabolites, or disease-specific mechanisms independently, and there remains a need for critical integration of phytochemical structure, microbial biotransformation pathways, metabolite formation, and host biological responses [5,12,14]. Moreover, the rapid expansion of multi-omics technologies has generated new evidence about microbial enzymatic pathways and phytochemical metabolism that requires evaluation alongside pharmacokinetic and human data [14,17].

Therefore, this narrative review aims to provide an integrated overview of the current evidence on the microbial biotransformation of dietary phytochemicals, the formation of gut-derived metabolites, and the molecular mechanisms linking these metabolites to human health. By combining evidence from phytochemistry, microbiology, metabolomics, and nutritional sciences, this review seeks to clarify the metabolic pathways connecting dietary phytochemicals with gut-derived metabolites, distinguish experimental mechanisms from clinically substantiated effects, identify evidence gaps, and highlight future research priorities in this rapidly evolving field.

2. Results

2.1. Major Classes of Dietary Phytochemicals

Dietary phytochemicals comprise a highly diverse group of naturally occurring bioactive compounds synthesised by plants as secondary metabolites involved in defence against pathogens, ultraviolet radiation, herbivores, and other environmental stresses. Although they are not considered essential nutrients, phytochemicals have attracted considerable scientific interest because of their potential contribution to human health through antioxidant, anti-inflammatory, immunomodulatory, antimicrobial, and metabolic regulatory activities. Increasing evidence indicates that some biological effects associated with phyto-

chemical intake may involve gut-derived metabolites, although the relative contributions of parent compounds, microbial products, and host metabolites remain incompletely defined [1,19,31].

The structural diversity of dietary phytochemicals largely determines their physicochemical properties, intestinal absorption, bioavailability, and susceptibility to microbial metabolism. Many phytochemicals occur naturally as glycosides, esters, polymers, or complex conjugates that are poorly absorbed in the upper gastrointestinal tract. Consequently, substantial quantities reach the colon intact, where they become substrates for the enzymatic activity of the gut microbiota. This metabolic interface between dietary phytochemicals and intestinal microorganisms represents a critical determinant of their biological fate and ultimately influences their physiological activity in the host [1,13,32]. Representative chemical structures of the principal dietary phytochemicals discussed in this review are presented in Figure 1.

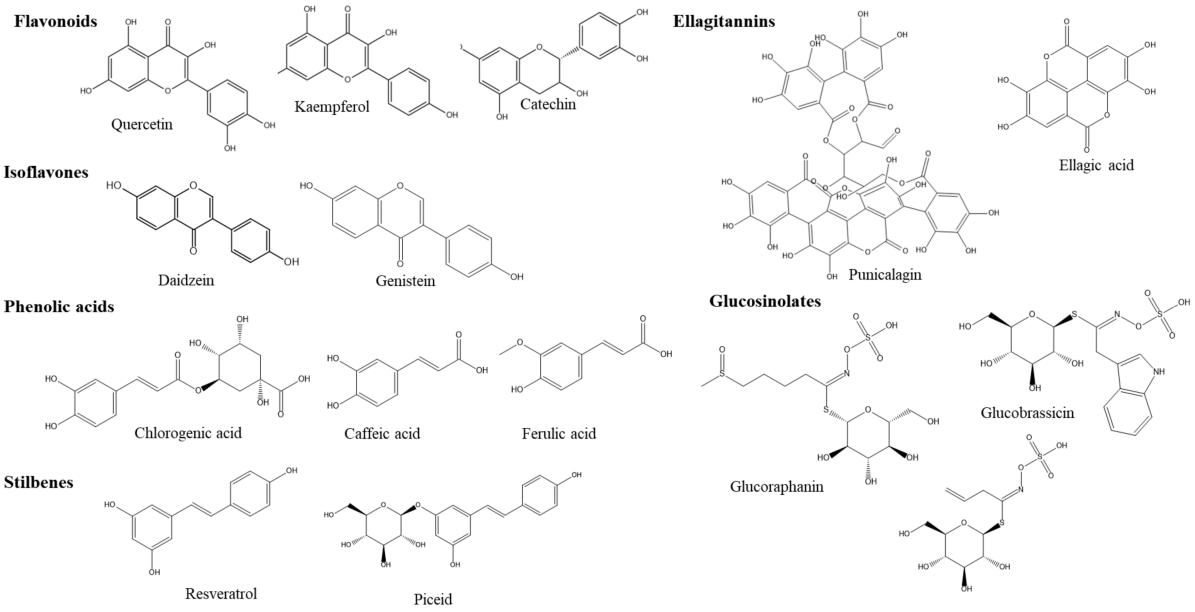


Figure 1. Representative chemical structures of selected dietary phytochemicals discussed in this review. Compound classes and representative examples were selected with reference to the published phytochemical literature [1–4].

Among dietary phytochemicals, polyphenols constitute the largest and most extensively investigated class. They include several structurally distinct subclasses, namely flavonoids (flavonols, flavones, flavanones, flavan-3-ols, anthocyanins, and isoflavones), phenolic acids, stilbenes, lignans, coumarins, and tannins. Polyphenols are widely distributed in fruits, vegetables, legumes, whole grains, tea, coffee, cocoa, nuts, olive oil, herbs, spices, and red wine, making them one of the principal sources of bioactive compounds in plant-based diets. Owing to their complex chemical structures, particularly the presence of glycosidic bonds and polymeric forms, small-intestinal absorption varies substantially across polyphenol subclasses and depends on chemical structure, food matrix, and host factors. Unabsorbed fractions may reach the colon, where microbial metabolism generates low-molecular-weight phenolic derivatives with pharmacokinetic and biological properties that can differ from those of their precursors [1,13,31].

A randomised human crossover intervention provides substrate-specific evidence for the flavan-3-ol pathway: monomeric (epi)catechins yielded substantially more urinary hydroxyphenyl-γ-valerolactones than oligomeric procyanidins at comparable polymer-derived intake. The authors estimated conversion of approximately 22% of catechins,

whereas conversion of the oligomeric substrates was limited. These observations should not be generalised to all flavonoid structures [33].

Carotenoids constitute another major class of dietary phytochemicals. These lipid-soluble tetraterpenoid pigments include carotenes, such as β-carotene and lycopene, and xanthophylls, including lutein, zeaxanthin, and β-cryptoxanthin. Carotenoids are abundant in brightly coloured fruits and vegetables, particularly carrots, tomatoes, pumpkins, sweet potatoes, leafy green vegetables, mangoes, and peppers. Some carotenoids act as provitamin A compounds, while others have been investigated for antioxidant-related properties and have been associated with the maintenance of visual function, immune competence, and cardiometabolic health. Although carotenoids are absorbed primarily in the small intestine owing to their lipophilic nature, the gut microbiota may indirectly influence carotenoid availability and host responses; direct microbial formation of specific carotenoid metabolites in humans remains poorly established, although these pathways remain considerably less characterised than those described for polyphenols [19,34].

Glucosinolates are sulphur-containing phytochemicals found predominantly in cruciferous vegetables, including broccoli, cabbage, cauliflower, Brussels sprouts, kale and rocket. Following plant-tissue disruption, endogenous myrosinase hydrolyses glucosinolates to products that may include isothiocyanates, nitriles and thiocyanates. Food processing can inactivate plant myrosinase; in that circumstance, microbial myrosinase-like activity may contribute to intestinal hydrolysis. The extent and profile of conversion depend on the substrate, processing conditions and microbial community. Accordingly, the detection of sulforaphane or erucin after consumption of cruciferous vegetables does not, by itself, establish that these products were formed by gut bacteria [19,35].

Evidence for glucosinolate transformation varies by bacterial strain and by the contribution of plant myrosinase. In pure-culture experiments, *Lactobacillus agilis* R16, *Enterococcus casseliflavus* CP1 and *Escherichia coli* VL8 showed distinct rates and product profiles when metabolising glucoraphanin, glucoiberin and glucoerucin [36]. In a human broccoli-sprout intervention ($n = 55$), sulforaphane and sulforaphane-nitrile metabolites varied between individuals and were associated with particular microbial taxa, without proving that those taxa produced all measured metabolites [37]. A separate randomised crossover trial ($n = 16$) showed higher urinary sulforaphane-metabolite recovery when mustard-seed myrosinase was added to a glucoraphanin-rich extract (39.8% versus 18.6% estimated conversion), demonstrating that enzyme source and formulation materially affect exposure [38].

Organosulfur compounds, mainly derived from Allium vegetables such as garlic (*Allium sativum*), onions (*Allium cepa*), leeks, and chives, represent another important group of dietary phytochemicals. The principal bioactive constituents include allicin, ajoene, diallyl sulphides, and S-allyl cysteine derivatives, which are generated following enzymatic conversion of alliin after tissue disruption. These compounds have been extensively investigated because of their antimicrobial, antioxidant, anti-inflammatory, cardioprotective, and anticancer properties. Although their chemical instability results in rapid transformation after ingestion, emerging evidence indicates that intestinal microorganisms may further metabolise organosulfur compounds, thereby influencing both their bioavailability and biological activity [19,39].

Other classes of dietary phytochemicals have also attracted increasing attention owing to their potential interactions with the gut microbiota. These include lignans, predominantly found in flaxseed, sesame seeds, and whole grains, which are converted into the mammalian lignans enterodiol and enterolactone by intestinal bacteria [34,40]. Among soy isoflavones, daidzein can undergo microbial conversion to equol and O-desmethylangolensin; these products are not formed to the same extent in all individuals and have distinct biological activities [41]. Additional phytochemical classes, including alkaloids, terpenoids,

saponins, phytosterols, and iridoids, are also increasingly recognised as substrates for microbial transformation, although their metabolic pathways remain comparatively less understood [19,34].

Despite their remarkable chemical diversity, these phytochemical classes share an important characteristic: the proportion reaching the colon varies by compound, formulation, food matrix, and host factors, where it is exposed to the extensive metabolic activity of the gut microbiota. Consequently, microbial biotransformation represents a central process determining the bioavailability and biological activity of many dietary phytochemicals. The major dietary sources, microbial biotransformation pathways, and principal gut-derived metabolites are summarised in Table 1.

Table 1. Major classes of dietary phytochemicals, representative compounds, dietary sources, microbial biotransformation, and principal gut-derived metabolites. Abbreviations: O-DMA, O-desmethylangolensin; SDG, secoisolariciresinol diglucoside.

Phytochemical Class	Representative Compounds	Major Dietary Sources	Predominant Microbial Biotransformation	Major Gut-Derived Metabolites	Key References
Flavonoids	Quercetin, kaempferol, catechins, epicatechin, hesperidin, naringin, anthocyanins	Fruits, berries, citrus fruits, onions, tea, cocoa, grapes	Deglycosylation, ring fission, dehydroxylation, demethylation	Phenylpropionic acids, phenylacetic acids, hydroxybenzoic acids, valerolactones	[1,31–34]
Ellagitannins	Punicalagin, ellagic acid	Pomegranate, walnuts, raspberries, strawberries	Hydrolysis and bacterial lactone opening, decarboxylation and dehydroxylation in successive steps	Urolithin intermediates (e.g., urolithin C); urolithin A after additional dehydroxylation by compatible bacteria	[42–44]
Isoflavones	Daidzein, genistein, glycitein	Soybeans and soy-derived foods	Deglycosylation, reduction, dehydroxylation	S-equol and O-DMA from daidzein; dihydrogenistein/5-hydroxyequol from genistein (species dependent)	[41,45]
Lignans	Secoisolariciresinol diglucoside (SDG), matairesinol	Flaxseed, sesame seeds, whole grains	Deglycosylation, demethylation, dehydroxylation	Enterodiol, enterolactone	[34,40]
Phenolic acids	Chlorogenic acid, caffeic acid, ferulic acid, gallic acid	Coffee, cereals, fruits, vegetables	Ester hydrolysis, reduction, decarboxylation	Hydroxyphenylpropionic acids, hydroxybenzoic acids	[1,13,46,47]
Stilbenes	Resveratrol, piceid	Grapes, red wine, peanuts	Deglycosylation, hydrogenation	Dihydroresveratrol, lunularin	[34,48]
Glucosinolates	Glucoraphanin, sinigrin, glucobrassicin	Broccoli, cabbage, kale, Brussels sprouts, cauliflower	Plant myrosinase hydrolysis; microbial myrosinase-like activity can contribute when plant enzyme is inactive	Sulforaphane and erucin (also formed through plant myrosinase); selected indole products	[19,35–38]

Table 1. *Cont.*

Phytochemical Class	Representative Compounds	Major Dietary Sources	Predominant Microbial Biotransformation	Major Gut-Derived Metabolites	Key References
Organosulfur compounds	Alliin, allicin, diallyl sulphides, S-allyl cysteine	Garlic, onion, leek	Enzymatic reduction and sulphur metabolism	Sulphur-containing metabolites	[19,39]
Carotenoids	β-Carotene, lycopene, lutein, zeaxanthin	Carrots, tomatoes, leafy vegetables, pumpkin	Limited direct microbial transformation; indirect modulation of bioavailability	Specific human gut-microbial carotenoid products remain unconfirmed	[19,34]
Terpenoids, saponins and phytosterols	Ginsenosides, β-sitosterol, glycyrrhizin	Medicinal plants, legumes, vegetable oils	Deglycosylation, hydrolysis, reduction	Minor bioactive derivatives (compound-dependent)	[12,34]

This metabolic interplay between plant-derived compounds and intestinal microorganisms provides the biological basis for understanding how structurally diverse phytochemicals converge into common gut-derived metabolites capable of modulating multiple molecular pathways and physiological processes. The following sections examine the principal microbial biotransformation mechanisms, the formation of gut-derived metabolites, and their implications for human health.

2.2. Microbial Biotransformation Mechanisms

The biological activity of dietary phytochemicals depends not only on their chemical structure but also on the extensive metabolic transformations they undergo within the gastrointestinal tract. Where absorption or digestion in the upper gastrointestinal tract is incomplete, phytochemical substrates may reach the colon owing to their complex molecular structures, poor aqueous solubility, or occurrence as glycosides, polymers, and other conjugated forms. Within the large intestine, these compounds become substrates for the enzymatic machinery of the gut microbiota, which catalyses a wide range of biotransformation reactions that profoundly influence their bioavailability, biological activity, and physiological effects [1,13,32,34].

Microbial biotransformation encompasses numerous enzymatic reactions that modify the physicochemical properties of phytochemicals, generating products with altered molecular structure and potentially different absorption and activity profiles. The principal reactions include deglycosylation, ester hydrolysis, ring cleavage, dehydroxylation, demethylation, decarboxylation, dehydrogenation, hydrogenation, reduction, oxidation, and deconjugation (Table 1). These reactions are catalysed by diverse bacterial enzymes, including glycosidases, esterases, reductases, decarboxylases, demethylases, and oxidoreductases, whose expression varies considerably among microbial species and individuals [1,19,32].

Among these reactions, deglycosylation can represent an early and important step for phytochemicals occurring as glycosides. Numerous dietary flavonoids, isoflavones, anthocyanins, and lignans occur naturally as glycosides, whose attached sugar moieties limit passive intestinal absorption. Microbial β-glucosidases and related glycosidases hydrolyse these glycosidic bonds, releasing the corresponding aglycones that can subsequently undergo further microbial metabolism or be absorbed by the host. Deglycosylation therefore represents a critical determinant of phytochemical bioavailability and subsequent metabolic fate [13,32]. Following deglycosylation, many phytochemicals undergo ring cleavage, one of the hallmark reactions of microbial metabolism. Aromatic ring cleavage can generate low-molecular-weight phenolic compounds whose absorption and activity profiles require

evaluation for each individual metabolite. Additional reactions, including dehydroxylation, demethylation, and decarboxylation, further modify molecular polarity, stability, and receptor affinity, producing metabolites that differ substantially from their parent compounds in both pharmacokinetic and pharmacodynamic characteristics [1,34]. Reduction and hydrogenation reactions also contribute significantly to microbial metabolism, particularly for compounds containing double bonds or carbonyl groups. For example, intestinal microorganisms catalyse the reduction of isoflavones, stilbenes, and other polyphenols, producing metabolites with altered biological activities. Likewise, ester hydrolysis plays an essential role in the metabolism of phenolic acids and related compounds by releasing free phenolic acids from esterified dietary forms [13,19].

For chlorogenic acid, a strain-resolved mechanism has been demonstrated: Bifidobacterium animalis subsp. lactis WC 0432 hydrolysed the caffeoyl ester to release caffeic acid, with feruloyl esterase Balat_0669 functionally characterised in a heterologous expression system [46]. In separate in vitro fermentations using faecal microbiota from nine individuals, hydrogenation, dehydroxylation and ester hydrolysis proceeded in different sequences and converged on 3-(3-hydroxyphenyl)propanoic acid. These observations provide direct evidence of interindividual variation in substrate-to-metabolite pathways rather than a uniform response attributable to one genus [47].

Although these enzymatic reactions are often described individually, microbial phytochemical metabolism is typically characterised by sequential and interconnected metabolic pathways involving multiple bacterial taxa. Consequently, the complete conversion of a single phytochemical frequently requires metabolic cooperation among different microbial species through processes known as cross-feeding. Such microbial interactions increase the diversity of gut-derived metabolites while contributing to the marked interindividual variability observed in phytochemical metabolism [12,34].

Several bacterial genera have been implicated in phytochemical biotransformation, although the metabolic capacity varies considerably between species and strains. Members of the genera Bacteroides, Bifidobacterium, Lactobacillus, Clostridium, Eggerthella, Gordonibacter, Eubacterium, and Blautia are among the microorganisms most frequently associated with the metabolism of dietary polyphenols and other phytochemicals. However, the complete repertoire of microbial enzymes responsible for many transformation pathways remains incompletely characterised, and numerous metabolites continue to be generated through pathways that are only partially understood [12,19,32,34].

For flavan-3-ols, isolated *Eggerthella lenta* strain rK3 reductively cleaved the C-ring of catechin and epicatechin, generating a diphenylpropanol intermediate. Flavonifractor plautii strain aK2, as well as the reference strain DSM 6740, subsequently converted this intermediate to a phenyl-γ-valerolactone and a related valeric acid. These experiments provide direct organism-specific evidence for sequential conversion, but downstream systemic exposure also depends on host conjugation and transport [49]. Across all pathways, enzyme assignment requires evidence stronger than a correlation between bacterial abundance and metabolite concentration.

Formation of enterolignans likewise requires complementary microbial activities. In a culture-based study, Bacteroides distasonis, *B. fragilis* and *B. ovatus* strains were among the organisms capable of deglycosylating secoisolariciresinol diglucoside (SDG) to secoisolariciresinol; strains of *Eubacterium limosum* and related species performed O-demethylation, while *Eggerthella lenta* or *Clostridium scindens* strains contributed to dehydroxylation. A distinct bacterial isolate catalysed oxidation of enterodiol to enterolactone. These strain-level observations document individual biochemical steps and should not be interpreted as proof that each species independently completes the entire pathway in vivo [50].

The isoflavone pathway is more fully characterised at the enzyme level. In Slackia isoflavoniconvertens, functionally characterised daidzein reductase (DZNR), dihydrodaidzein reductase (DHDR) and tetrahydrodaidzein reductase (THDR) catalyse successive reduction steps leading from daidzein through dihydrodaidzein and tetrahydrodaidzein to S-equol. Genistein is a distinct substrate: the same organism can reduce genistein to dihydrogenistein and has been associated with 5-hydroxyequol production, but genistein should not be described as a direct precursor of equol. Importantly, in recombinant enzyme assays DZNR reduced genistein to dihydrogenistein, whereas the corresponding downstream 5-hydroxyequol reaction was not reproduced with isolated DHDR and THDR, illustrating the importance of separating whole-cell pathways from the activity demonstrated for individual enzymes [45].

The ellagitannin-to-urolithin pathway illustrates why a substrate–enzyme–species assignment is preferable to a genus-level statement. Hydrolysis of dietary ellagitannins releases ellagic acid, which undergoes successive bacterial lactone-opening and dehydroxylation reactions. Gordonibacter urolithinfaciens and related organisms contribute to intermediate urolithin formation, but production of the final metabolite urolithin A cannot be attributed to Gordonibacter alone. *Enterocloster bolteae*, *E. asparagiformis* and *E. citroniae* have been shown to convert urolithin C to urolithin A. In E. bolteae, a substrate-inducible ucdCFO operon encoding a predicted molybdopterin-dependent dehydroxylase complex provides direct genetic and functional evidence for this specific step [43,51]. This multi-organism sequence also helps explain the existence of urolithin-producing and non-producing metabotypes.

The additional regioselectivity of the urolithin pathway has been demonstrated at operon level. Pidgeon and colleagues identified an inducible 10-hydroxy urolithin dehydroxylase operon (uxd) in *Enterocloster asparagiformis*, *E. citroniae* and *E. pacaense*, whereas the tested *E. bolteae* lacked the same conversion pattern. This complements the previously characterised 9-hydroxy dehydroxylation system (ucd) and provides evidence for cooperative conversion of intermediates released by *Gordonibacter* species [52].

Figure 2 summarises the sequence from dietary phytochemical precursors and strain-dependent microbial transformations to host conjugation and possible translational applications. The diagram distinguishes directly derived catabolites from broader microbiota-associated responses.

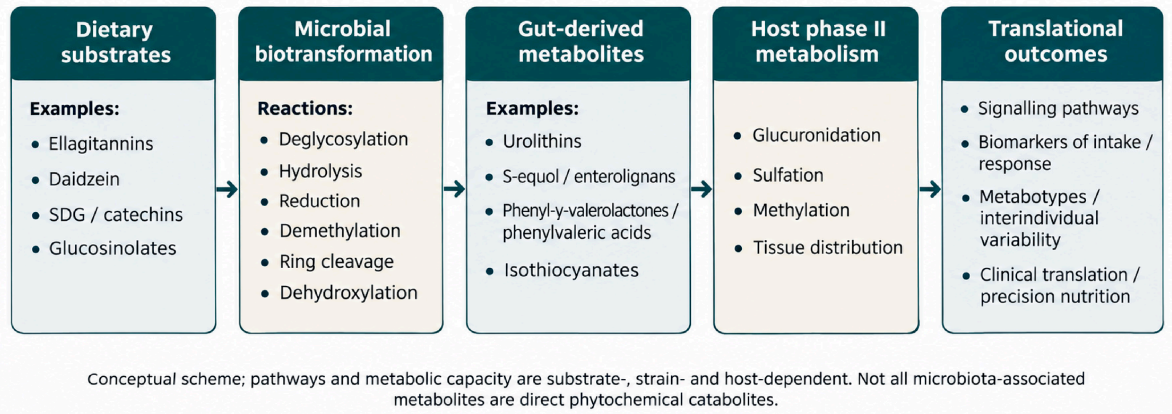


Figure 2. Evidence-informed conceptual overview of dietary phytochemical biotransformation, from precursor substrates and bacterial reactions to microbial catabolites, host phase II metabolism and translational questions. The scheme integrates established reaction classes and representative pathways from the literature [1,12,13,34,43,45]. Specific transformations depend on substrate, microbial strain and host context; pathways shown should not be interpreted as universal. Abbreviations: SDG, secoisolariciresinol diglucoside. The conceptual illustration was created with assistance from ChatGPT (OpenAI, GPT-6.2) and was critically reviewed by the authors.

Collectively, these microbial transformations modify the structures of dietary phytochemicals and can generate a broad spectrum of gut-derived metabolites with distinct physicochemical characteristics and biological activities. The diversity of these metabolites provides the mechanistic basis for understanding how structurally heterogeneous phytochemicals may converge into common biological pathways that influence host physiology. Nevertheless, despite considerable advances in characterising microbial biotransformation reactions, the enzymatic repertoire responsible for many of these pathways remains incompletely understood, and substantial interindividual variability continues to challenge the prediction of metabolite formation and biological responses. Further characterisation of microbial enzymes and metabolic networks will be essential to establish robust structure–metabolism–function relationships. The principal microbial biotransformation reactions, associated enzymes, representative microbial taxa, phytochemical substrates, and resulting metabolites are summarised in Table 2. The following section describes the principal classes of gut-derived metabolites generated through microbial biotransformation and their relevance to human health.

Table 2. Principal microbial biotransformation reactions involved in the metabolism of dietary phytochemicals. Abbreviations: DHDR, dihydrodaidzein reductase; DZNR, daidzein reductase; DSM, German Collection of Microorganisms and Cell Cultures (strain designation); THDR, tetrahydrodaidzein reductase; UcdCFO, urolithin C dehydroxylase enzyme complex; uroC and uroA, urolithin C and urolithin A, respectively.

Biotransformation Reaction	Principal Microbial Enzymes	Representative Microbial Taxa	Major Phytochemical Substrates	Representative Gut-Derived Metabolites	Key References
Deglycosylation	β-Glucosidases, α-rhamnosidases, β-galactosidases	Bifidobacterium, Lactobacillus, Bacteroides, Enterococcus	Flavonoid glycosides, isoflavones, anthocyanins, lignans	Aglycones (quercetin, daidzein, genistein), ellagic acid	[1,13,32]
Ester hydrolysis	Esterases, tannases	Lactobacillus, Bifidobacterium, Enterococcus	Chlorogenic acid, gallotannins, ellagitannins	Caffeic acid, gallic acid, ellagic acid	[1,13,46,47]
Ring cleavage	C-ring reductive cleavage and downstream conversion (activities identified in isolates)	Eggerthella lenta rK3; Flavonifractor plautii aK2 and DSM 6740	Catechin/epicatechin	Diphenylpropanol intermediate → phenyl-γ-valerolactone	[49]
Dehydroxylation	Dehydroxylases	Clostridium, Eubacterium, Eggerthella	Phenolic acids, flavonoids	Dehydroxylated phenolic metabolites	[1,19]
Demethylation	O-Demethylases	Eubacterium, Blautia, Eggerthella	Lignans, flavonoids, phenolic acids	Demethylated phenolic derivatives	[12,34]
Decarboxylation	Phenolic acid decarboxylases	Lactobacillus, Bacillus, Enterococcus	Hydroxycinnamic acids (ferulic, caffeic, p-coumaric acids)	Vinyl phenols, ethyl phenols	[13,34]
Reduction/Hydrogenation	DZNR, DHDR, THDR (characterised for daidzein); other reductases substrate dependent	Slackia isoflavoniconvertens; other strain-dependent reducers	Daidzein; genistein (distinct pathway)	Daidzein → S-equol; genistein → dihydrogenistein/5-hydroxyequol	[45]

Table 2. *Cont.*

Biotransformation Reaction	Principal Microbial Enzymes	Representative Microbial Taxa	Major Phytochemical Substrates	Representative Gut-Derived Metabolites	Key References
Lactone opening and sequential dehydroxylation	Lactone-opening and dehydroxylating activities; UcdCFO for uroC → uroA	Gordonibacter spp. (ellagic-acid intermediates); Enterocloster bolteae, E. asparagiformis and E. citroniae (urolithin C → A)	Ellagic acid and urolithin C	Urolithin intermediates; uroC → uroA	[43,51,52]
Desulfation and deconjugation	Sulfatases, β-glucuronidases	Bacteroides, Clostridium, Escherichia	Sulfated and glucuronidated phytochemical metabolites	Free aglycones and secondary metabolites	[12,34]

2.3. Formation of Gut-Derived Metabolites

Microbial biotransformation of dietary phytochemicals gives rise to a diverse array of low-molecular-weight metabolites that frequently differ substantially from their parent compounds in terms of chemical structure, bioavailability, biological activity, and tissue distribution. Beyond representing degradation products, some gut-derived metabolites have biological activities that may contribute to the effects associated with phytochemical-containing foods. Their molecular size, polarity, conjugation, and transport characteristics may differ from those of the parent compounds, and systemic exposure varies considerably across metabolites [1,19,53].

The diversity of microbial metabolites reflects both the chemical structure of dietary precursors and the functional capacities of the microbiota. A single compound may undergo successive reactions involving several organisms, whereas different dietary molecules can yield partially overlapping phenolic catabolites. This convergence is a chemical observation and does not, on its own, demonstrate equivalent physiological effects of different foods. Table 3 summarises the main substrate-to-metabolite associations, while the following text distinguishes direct formation from broader changes in microbiota composition or activity [12,34].

Table 3. Representative metabolites associated with microbial biotransformation of dietary phytochemicals, microbial taxa involved, and reported experimental biological relevance. Abbreviations: O-DMA, O-desmethylangolensin; spp., multiple species within a genus.

Parent Phytochemical	Major Dietary Sources	Principal Gut-Derived Metabolites	Representative Microbial Taxa	Reported Biological Relevance	Key References
Ellagitannins	Pomegranate, walnuts, berries	Urolithins A–D	Gordonibacter spp. (upstream intermediates); Enterocloster spp. (documented urolithin C → A step); activities are strain-dependent	Documented microbial formation; preclinical effects on barrier function, mitochondrial pathways and inflammation; clinical outcome evidence remains limited	[43,52,54]
Isoflavones	Soybeans	S-equol and O-DMA from daidzein; 5-hydroxyequol pathway from genistein	Slackia isoflavoniconvertens (characterised daidzein reductases); alternative O-DMA-producing communities not assigned to one taxon	Estrogenic activity, antioxidant effects	[41,45]

Table 3. *Cont.*

Parent Phytochemical	Major Dietary Sources	Principal Gut-Derived Metabolites	Representative Microbial Taxa	Reported Biological Relevance	Key References
Lignans	Flaxseed, sesame	Enterodiol, enterolactone	Eggerthella, Clostridium	Endocrine modulation, cardiometabolic health	[40]
Flavonoids	Tea, cocoa, berries, citrus	Phenolic acids, valerolactones	E. lenta rK3 and F. plautii aK2 (sequential catechin transformation demonstrated in isolates); other taxa substrate-dependent	Antioxidant and anti-inflammatory activity	[1,33,55]
Phenolic acids	Coffee, cereals	Hydroxyphenylpropionic acids	Multiple taxa	Metabolic regulation	[13,46,47]
Glucosinolates	Broccoli, cabbage	Sulforaphane and erucin (plant and/or microbial myrosinase)	Myrosinase-producing bacteria	Chemoprotective mechanisms (experimental)	[35–38]
Stilbenes	Grapes, wine	Dihydroresveratrol	Slackia spp.	Potential cardiometabolic effects (preclinical)	[34]

For the purposes of this review, three levels of evidence are distinguished: (i) direct formation of a specified phytochemical-derived catabolite demonstrated through an identified precursor and microbial conversion system; (ii) indirect microbiome responses, such as altered short-chain fatty acid production or tryptophan-derived indole profiles after a dietary intervention, without proof that the products originate from the phytochemical itself; and (iii) host-derived conjugates (including glucuronides and sulfates) formed after absorption of microbial products. These categories are mechanistically distinct and should not be pooled as equivalent evidence of direct phytochemical biotransformation.

Urolithins are among the best-characterised direct catabolites of dietary ellagitannins and ellagic acid, found in pomegranates, berries and walnuts. Ellagitannin hydrolysis releases ellagic acid, followed by bacterial lactone opening and successive dehydroxylation steps. Isolates assigned to Gordonibacter, together with other urolithin-associated bacteria, can generate intermediates, but their presence alone does not demonstrate complete conversion to urolithin A. Experimental work has identified Enterocloster species capable of converting urolithin C into urolithin A, including a characterised ucdCFO-associated dehydroxylation step. Thus, individual reactions, metabolite endpoints and strains should be reported separately rather than attributing formation of all urolithins A–D to a single genus [43,44,51,54].

Isoflavones provide a comparatively well-characterised example of species-dependent microbial metabolism. Daidzein may undergo successive reductions to dihydrodaidzein, tetrahydrodaidzein and ultimately S-equol in individuals carrying an appropriate enzymatic microbiota; O-desmethylangolensin represents an alternative product. In contrast, genistein can yield dihydrogenistein and, under specific whole-cell conditions, 5-hydroxyequol, rather than S-equol. The genes encoding DZNR, DHDR and THDR have been functionally studied in Slackia isoflavoniconvertens, whereas differences in metabotype affect exposure in humans [41,45].

Plant lignans are converted by specialised intestinal microorganisms into enterodiol and enterolactone. Individual isolates have been demonstrated to catalyse the deglycosylation, O-demethylation, dehydroxylation and dehydrogenation steps, but no single named genus should be assumed to perform the complete sequence. The requirement for cross-feeding

and strain-specific activities is supported by the isolation and characterisation of SDG-transforming bacteria [40,50].

Microbial metabolism of flavonoids produces an extensive range of low-molecular-weight phenolic acids, including hydroxyphenylpropionic acids, hydroxyphenylacetic acids, hydroxybenzoic acids, and valerolactones. Some of these metabolites are detectable in systemic circulation and may contribute to responses following the consumption of flavonoid-rich foods such as tea, cocoa, berries, and citrus fruits [1,13].

Human urinary phenyl-γ-valerolactone conjugates also have translational value as potential biomarkers of flavan-3-ol exposure. A randomised crossover study combined with observational data evaluated their performance after apple, cocoa and tea consumption, emphasising that these conjugates report exposure rather than proving a therapeutic effect or defining the site of microbial synthesis [55].

Although polyphenol-derived metabolites have received the greatest scientific attention, microbial metabolism also generates bioactive compounds from other phytochemical classes. Glucosinolates may yield isothiocyanates, including sulforaphane and erucin, through plant myrosinase or microbial enzymatic activity, depending on food processing and intestinal conditions; microbial metabolism of stilbenes can produce dihydroresveratrol and related derivatives. Likewise, organosulfur compounds undergo further microbial transformation, generating sulphur-containing metabolites that may contribute to their biological activities. However, compared with polyphenols, these metabolic pathways remain comparatively less characterised and represent important areas for future investigation [19,35,39].

Recent advances in untargeted metabolomics have substantially expanded the catalogue of gut-derived metabolites identified in biological samples. Nevertheless, a considerable proportion of the metabolites detected following phytochemical consumption remain structurally uncharacterised, and many of the microbial enzymes and metabolic pathways responsible for their formation have yet to be identified. Consequently, the gut metabolome should be regarded as a dynamic and continuously evolving metabolic network shaped by interactions between diet, microbial ecology, and host physiology [12,14].

Collectively, these findings demonstrate that microbial metabolism can transform diverse dietary phytochemicals into numerous metabolites, some of which exhibit activity towards molecular targets in experimental systems. Understanding the formation, bioavailability, and biological functions of these gut-derived metabolites is therefore fundamental for elucidating the mechanisms through which phytochemical-rich diets influence human health. Despite substantial progress, many gut-derived metabolites remain structurally or functionally insufficiently characterised, and the microbial enzymes responsible for their formation have yet to be fully identified. Addressing these knowledge gaps will be essential to establish robust structure–metabolism–function relationships and improve the prediction of biological responses to phytochemical-rich diets. The following section examines the principal molecular and cellular signalling pathways regulated by these microbial metabolites.

2.4. Molecular and Cellular Signalling Pathways

Molecular activity should be assigned to an identified metabolite, model and experimental exposure rather than inferred from the parent dietary phytochemical. For urolithin A, preclinical work has demonstrated an AhR–Nrf2-dependent increase in epithelial tight-junction proteins and attenuation of experimental colitis, while a separate in vitro/in vivo study linked this metabolite to Nrf2-associated responses during myocardial fibrosis [56,57]. These studies demonstrate pathway modulation, not necessarily direct binding to Nrf2 or clinical benefit following habitual consumption of ellagitannin-rich foods. Sulforaphane can

also activate Nrf2, but its formation may involve plant myrosinase rather than an exclusively microbial reaction [58].

NF-κB regulation has been investigated using specific urolithins and other phenolic derivatives. Urolithin A inhibited NF-κB activation in lipopolysaccharide-stimulated bone-marrow-derived macrophages, while urolithin C suppressed inflammatory signalling in an experimental RAW 264.7 macrophage model [59,60]. Such assays should be distinguished from trials demonstrating disease prevention. Protocatechuic acid has also been reported to modify TLR4/p38 MAPK/NF-κB-associated responses in heat-stressed broilers, an animal model whose physiological transferability to humans requires assessment [61].

Metabolite and pathway assignments can also be context dependent. In LPS-stimulated RAW264 macrophages, urolithin A inhibited PI3K/Akt/NF-κB and JNK/AP-1 signalling together with inflammatory mediator production [62]. Comparative experiments in macrophages and neutrophils found that free urolithin A, but not the tested glucuronide conjugates, suppressed selected inflammatory readouts [63]. Separately, free urolithins at 1–15 μmol/L reduced 5-lipoxygenase- and cyclooxygenase-2-associated eicosanoids in activated human leukocytes, while the tested sulfate and glucuronide forms were inactive in those assays [64]. These findings document model-specific pathway inhibition and compound-form effects; they do not establish systemic efficacy in humans.

AMPK-related signalling provides a further example of a metabolite-specific pathway. Urolithin A promoted mitophagy through AMPK-dependent mechanisms in an experimental intervertebral-disc model, and a 2026 mouse study of heart failure with preserved ejection fraction linked administration of urolithin A to increased AMPK phosphorylation, reduced mTOR activity, restored ULK1 signalling and improved indices of mitochondrial function [65,66]. These findings do not establish that the effective experimental dose is attained from dietary precursor intake. Different studies of protocatechuic acid have reported AMPK/mTOR-related glucose responses in experimental models [67].

Peroxisome proliferator-activated receptor gamma (PPARγ) is relevant to the isoflavone pathway: daidzein and its metabolite equol enhanced PPARγ transcriptional activity in 3T3-L1 adipocytes, together with changes in adipocyte differentiation and glucose-transport markers [68]. This is evidence of transcriptional pathway modulation in a cellular model, not proof of direct receptor binding in humans. In cardiovascular models, urolithin A has also been associated with PI3K/Akt signalling during ischaemia/reperfusion injury, while SIRT1/PGC-1α-related responses have been reported in oxidatively stressed mesenchymal stem cells [69,70].

The aryl hydrocarbon receptor (AhR) illustrates the need to establish the dietary origin of a metabolite before assigning a mechanism. In epithelial and experimental colitis models, urolithin A, a documented ellagitannin-derived microbial catabolite, increased AhR–Nrf2-related responses and tight-junction protein expression [56]. In contrast, indole-3-aldehyde and several other AhR-active indoles originate principally from microbial tryptophan metabolism. Their activity cannot be cited as evidence of direct phytochemical conversion merely because they are influenced by a plant-rich diet [21,71]. Similarly, short-chain fatty acids mainly derive from fermentation of dietary carbohydrates, and their levels after phytochemical interventions are better classified as contextual microbiome responses than as direct phytochemical catabolites.

The evidence therefore supports several metabolite-specific signalling responses rather than a universal mechanism of action. Table 4 identifies the tested chemical species, experimental models and primary mechanistic studies where available. Modulation of Nrf2, NF-κB, AMPK, PPARγ or AhR does not necessarily imply direct ligand binding to that protein. Selected metabolite-specific signalling responses and the experimental models in which they were observed are illustrated in Figure 3.

Table 4. Molecular and cellular signalling pathways reported to respond to selected metabolites in experimental studies. Abbreviations: AhR, aryl hydrocarbon receptor; AMPK, AMP-activated protein kinase; HFpEF, heart failure with preserved ejection fraction; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; mTOR, mechanistic target of rapamycin; NF-κB, nuclear factor kappa B; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1 alpha; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; PPARγ, peroxisome proliferator-activated receptor gamma; SIRT1, sirtuin 1; TLRs, Toll-like receptors; ULK1, Unc-51-like autophagy activating kinase 1.

Signalling Pathway	Tested Metabolite(S)	Measured Mechanistic Readout	Experimental Evidence and Interpretation	Primary References
Nrf2	Urolithin A; sulforaphane (plant and/or microbial origin)	AhR/Nrf2-dependent barrier markers; Nrf2-related antioxidant proteins	Cell and animal models; free compound, not established clinical target engagement	[56–58]
NF-κB	Urolithin A and urolithin C	Reduced NF-κB activation/inflammatory signalling	Macrophage cell models; no demonstrated clinical efficacy	[59,60,62–64]
AMPK	Urolithin A; protocatechuic acid	AMPK phosphorylation; mTOR–ULK1 and mitophagy readouts	Cell/animal studies, including HFpEF mice	[65–67]
PPARγ	S-equol and daidzein	PPARγ reporter/transcriptional activity; adipocyte markers	C3H10T1/2 differentiation assays and 3T3-L1 PPARγ reporter assays; free equol tested at μmol/L levels; no direct receptor-binding demonstration	[68]
PI3K/Akt	Urolithin A	PI3K/Akt-associated survival pathway	Cardiac ischaemia/reperfusion animal/cell model; opposite PI3K/Akt inhibition in LPS-stimulated macrophages [62]	[62,69]
MAPK	Protocatechuic acid	TLR4/p38 MAPK/NF-κB-associated readouts	Heat-stressed broilers (animal model)	[61]
AhR	Urolithin A (ellagitannin-derived); selected tryptophan-derived indoles [contextual, not direct phytochemical catabolites]	AhR–Nrf2 epithelial response; microbial indole–AhR association	Cell/animal gut barrier models; distinguish precursor origin	[56,71]
TLRs	Protocatechuic acid; urolithin A	TLR4-associated MAPK/NF-κB response	Animal model/macrophage cells; pathway modulation	[59,61]
mTOR/SIRT1	Urolithin A	AMPK–mTOR–ULK1; SIRT1/PGC-1α-related changes	Cardiac and stem-cell preclinical models	[66,70]

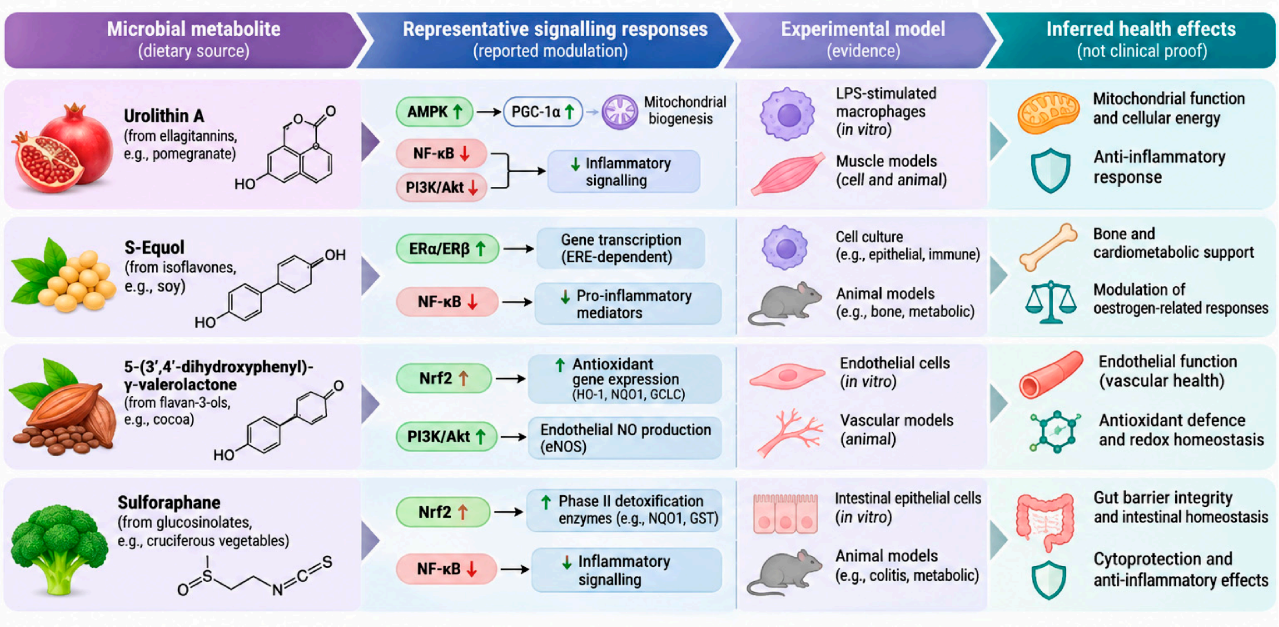


Figure 3. Illustrative experimental signalling responses to selected microbial phytochemical catabolites and related dietary compounds. Representative mechanistic and model-specific evidence was considered from primary investigations [56,58–60,62,65,68]; flavan-3-ol catabolite formation and biomarker evidence are addressed separately [55]. The sulforaphane panel does not imply exclusively microbial formation, and the phenyl-γ-valerolactone pathway arrows are conceptual rather than proof of direct target engagement by this specific metabolite. Pathway modulation does not establish direct receptor binding or clinical efficacy. Abbreviations: AMPK, AMP-activated protein kinase; eNOS, endothelial nitric oxide synthase; ERα/ERβ, oestrogen receptors alpha/beta; ERE, oestrogen response element; GCLC, glutamate-cysteine ligase catalytic subunit; GST, glutathione S-transferase; HO-1, haem oxygenase 1; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa B; NO, nitric oxide; NQO1, NAD(P)H quinone oxidoreductase 1; Nrf2, nuclear factor erythroid 2-related factor 2; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator 1 alpha; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B. The conceptual illustration was created with assistance from ChatGPT (OpenAI, GPT-6.2) and was critically reviewed by the authors.

2.5. Implications for Human Health

Microbial biotransformation has fundamentally reshaped current understanding of how dietary phytochemicals influence human health. Rather than acting solely through their native chemical structures, many phytochemicals undergo extensive microbial metabolism within the colon, generating gut-derived metabolites with improved bioavailability and distinct biological activities. These metabolites constitute one component of the interface between diet, the gut microbiota, and host physiology, linking microbial metabolism to multiple biological processes relevant to health and disease [19,72].

Experimental evidence suggests that selected gut-derived metabolites may influence multiple physiological systems through the coordinated modulation of molecular and cellular signalling pathways described in the previous section. One of the most consistently reported outcomes is the maintenance of intestinal homeostasis. Microbial metabolites contribute to preserving epithelial barrier integrity by regulating tight junction proteins, stimulating mucus production, and reducing intestinal permeability. These actions limit the translocation of bacterial endotoxins into the systemic circulation while promoting immune tolerance and reducing chronic low-grade inflammation, thereby supporting gastrointestinal health [12,18,19].

Experimental studies have also reported effects on pathways relevant to cardiometabolic health. Through the regulation of oxidative stress, inflammatory signalling, glucose home-

ostasis, lipid metabolism, and mitochondrial function, gut-derived metabolites such as urolithins, equol, phenolic acids, and isothiocyanates have shown protective effects in experimental models of obesity, insulin resistance, type 2 diabetes mellitus, and cardiovascular disease. These findings suggest potential mechanisms that may contribute to epidemiological associations between plant-rich dietary patterns and cardiometabolic outcomes [21,23,72].

The gut–brain axis represents another major area in which microbial phytochemical metabolism appears to play a significant role. Experimental studies indicate that several microbial metabolites influence neuroinflammation, oxidative stress, mitochondrial function, neuronal survival, and synaptic plasticity through immune, endocrine, and neural communication pathways. Some metabolites may also cross the blood–brain barrier, whereas others exert indirect effects through peripheral immune modulation. Although these observations support a potential contribution of microbial metabolism to neuroprotection and healthy cognitive ageing, clinical validation remains limited and requires further investigation [29,73,74].

Evidence for access to neural tissue is similarly metabolite-specific. After experimental dietary exposures in animal models, a sulfated 5-(hydroxyphenyl)-γ-valerolactone was detected in brain tissue by mass spectrometry. Identification and low abundance of the analyte do not demonstrate a neuroprotective effect or comparable human brain exposure [75].

Beyond metabolic and neurological pathways, selected gut-derived metabolites have been investigated for their potential immunomodulatory effects by modulating cytokine production, macrophage polarisation, T-cell differentiation, and innate immune responses. These immunomodulatory properties may contribute to the prevention of chronic inflammatory disorders and the maintenance of immune homeostasis. In parallel, several microbial metabolites have emerged as promising mediators of healthy ageing, particularly through their capacity to improve mitochondrial quality control, stimulate mitophagy, attenuate cellular senescence, and increase resistance to oxidative stress. Urolithin A represents one of the most extensively studied examples owing to its reported effects on mitochondrial function and age-related physiological decline [12,16,22].

Collectively, these observations suggest that the effects associated with plant-rich dietary patterns, including the Mediterranean diet, may in part reflect microbial metabolite production alongside the combined influence of nutrients, food matrices, and host factors. This emerging paradigm emphasises that health outcomes arise from dynamic interactions among dietary composition, gut microbial metabolism, and host physiology rather than from isolated dietary compounds [19,53,72].

Despite these advances, the strength of the available evidence varies considerably across research models. Most mechanistic knowledge originates from in vitro systems and animal models, particularly mice, which have been instrumental in demonstrating how phytochemicals such as berberine, resveratrol, Gynostemma pentaphyllum polysaccharides, schisandrin B, trilobatin, and red radish sprouts modify gut microbiota composition, intestinal barrier integrity, inflammatory signalling, tryptophan metabolism, and gut–brain communication [27,28,76–79].

Similarly, rat studies have demonstrated that dietary interventions including rice bran and whole rye have been associated with changes in gut microbiota composition, short-chain fatty acid production, and intestinal markers in experimental models [80,81]. Additional animal models, including poultry and agricultural species, have further expanded current knowledge regarding microbial metabolism and detoxification pathways [82,83].

In contrast, human evidence remains comparatively limited, although it is expanding rapidly. Human observational and intervention studies examining Mediterranean dietary patterns, oats, or pomegranate products have reported changes in gut microbiota composi-

tion or metabolite profiles; however, designs and outcomes differ across studies [26,84,85]. Clinical intervention studies have similarly demonstrated that dietary strategies such as rice bran supplementation can modify microbial metabolism and increase the production of beneficial metabolites in humans [86]. Furthermore, emerging evidence links Mediterranean diet-associated microbial signatures with improved cognitive performance and slower cognitive decline, which is consistent with, but does not establish, a causal role for microbial metabolism in gut–brain communication [26,87]. Nevertheless, the limited number of well-controlled clinical trials and the marked interindividual variability in gut microbiota composition continue to constrain the translation of experimental findings into personalised dietary recommendations.

Direct human intervention data remain heterogeneous. In a randomised pomegranate-extract study involving 49 overweight or obese participants, changes in selected cardiovascular risk biomarkers differed by urolithin-producing metabotype, with the most pronounced lipid responses reported in the UM-B subgroup [88]. Separately, a four-month randomised trial of directly administered urolithin A (500 or 1000 mg/day) in 88 middle-aged adults reported improvement in selected secondary muscle-function outcomes without significant improvement in peak power output, its primary endpoint [89]. These studies involve different interventions and cannot establish the same clinical effects after habitual consumption of dietary precursors.

Overall, current evidence supports microbial biotransformation as a relevant mechanism connecting dietary phytochemicals with host physiology, while its relative contribution to clinical outcomes remains uncertain. However, further longitudinal cohort studies, standardised dietary intervention trials, and integrated multi-omics approaches are required to establish causal relationships, identify predictive microbial metabotypes, and facilitate the implementation of precision nutrition strategies. The principal physiological implications of gut-derived phytochemical metabolites, together with the current level of evidence, major research needs, and supporting references, are summarised in Table 5.

Table 5. Reported physiological effects associated with selected gut-derived metabolites and the available types of evidence. Abbreviations: SCFAs, short-chain fatty acids.

Physiological System or Outcome	Representative Gut-Derived Metabolites	Principal Biological Effects	Current Level of Evidence	Major Research Needs	Key References
Intestinal homeostasis	Urolithins and phenolic acids (direct catabolites); SCFAs and many indoles (contextual products from other substrates)	Strengthening of epithelial barrier integrity; regulation of tight junction proteins and mucus production; reduced intestinal permeability and endotoxaemia; promotion of immune tolerance	Mechanistic evidence from in vitro and animal models; increasing but still limited human evidence	Long-term human interventions evaluating barrier function, microbial metabolism, and clinically relevant gastrointestinal outcomes	[12,18,19,63,64,81]
Cardiometabolic health	Urolithins, equol, phenolic acids, isothiocyanates	Improved glucose homeostasis, insulin sensitivity, lipid metabolism, endothelial function, and mitochondrial activity; attenuation of oxidative stress and inflammation	Predominantly preclinical evidence; growing observational and intervention evidence in humans	Large randomised controlled trials; determination of effective doses; assessment of metabolite exposure and hard clinical outcomes	[21,23,72,84,88]

Table 5. *Cont.*

Physiological System or Outcome	Representative Gut-Derived Metabolites	Principal Biological Effects	Current Level of Evidence	Major Research Needs	Key References
Gut–brain axis and neuroprotection	Urolithins and phenolic catabolites (direct); selected indoles (contextual tryptophan-derived products)	Reduced neuroinflammation and oxidative stress; improved mitochondrial function, neuronal survival, synaptic plasticity, and cognitive signalling	Predominantly supported by mechanistic and animal studies; emerging observational human evidence	Controlled clinical trials integrating cognition, microbial metabotypes, circulating metabolites, and neurobiological biomarkers	[26,27,29,73–75,90,91]
Immune regulation	Urolithins, phenolic acids, isothiocyanates; some indoles are contextual tryptophan-derived products	Modulation of cytokine production, macrophage polarisation, T-cell differentiation, and innate immune signalling; attenuation of chronic inflammatory responses	Experimental and mechanistic evidence; limited clinical validation	Human studies combining immune phenotyping, microbiome analysis, and targeted metabolomics; clarification of context-dependent pro- and anti-inflammatory effects	[12,22,72]
Healthy ageing	Urolithin A and other urolithins, phenolic metabolites	Enhancement of mitochondrial quality control and mitophagy; reduction in cellular senescence; improved resistance to oxidative stress and preservation of functional capacity	Strong mechanistic and preclinical evidence; early translational and clinical evidence	Longitudinal trials assessing physical function, frailty, cognitive ageing, metabolite exposure, and clinically meaningful ageing outcomes	[12,16,54,89]
Dietary patterns and systemic health	Mixed dietary catabolites, including phenolics, urolithins and enterolignans; SCFAs/indoles are contextual microbiome responses	Coordinated regulation of intestinal, metabolic, immune, cardiovascular, and neurological processes through interconnected signalling networks	Consistent observational associations; intervention evidence is increasing but heterogeneous	Standardisation of dietary interventions; investigation of whole foods and phytochemical interactions; assessment of sustained dietary exposure	[26,84–87]
Precision nutrition and personalised healthcare	Metabolite profiles determined by individual microbial metabotypes	Prediction of individual responses to phytochemical-rich foods; identification of microbial and metabolic biomarkers; development of personalised dietary strategies	Emerging evidence based mainly on observational, metabolomic, and multi-omics studies	Validation of microbial metabotypes; integration of metagenomics and metabolomics; reproducible predictive models; prospective personalised interventions	[12,16,19,55,72,88,92]

2.6. Pharmacokinetics, Host Conjugation and Physiological Relevance

Formation of a microbial metabolite in the colon is only the first step towards pharmacological relevance. Absorption, intestinal and hepatic first-pass metabolism, plasma protein binding, tissue transport, enterohepatic recycling, and renal elimination determine the exposure of host tissues. For many microbial phenolic catabolites, plasma contains substantial amounts of glucuronide and sulfate conjugates rather than the free aglycone tested in mechanistic assays. Data obtained after enzymatic deconjugation measure total metabolite equivalents and must not be presented as the circulating concentration of unconjugated compound [93,94].

Conjugation is particularly important for the equol and urolithin pathways. After direct administration of purified S-equol in human pharmacokinetic studies, less than 1% of circulating total S-equol was unconjugated, illustrating why total equol concentrations must not be treated as free agonist exposure [95]. In experimental immune-cell assays, glucuronides of urolithin A, isourolithin A and urolithin B lacked selected anti-inflammatory

effects observed with their corresponding free forms [63]. However, an experimental inflammation model demonstrated local tissue deconjugation of urolithin A glucuronide, indicating that systemic conjugate predominance does not exclude context-specific liberation of the free compound [96].

After oral pomegranate extract, plasma urolithin A conjugates were reported with a delayed appearance, whereas unconjugated urolithin A was measurable in only a subset of participants; this observation is consistent with microbiome-dependent formation and subsequent host phase-II conjugation [93]. More generally, human intervention work has identified distinct urolithin-producing metabotypes following exposure to ellagitannin-rich foods [44]. In contrast, studies administering purified urolithin A directly bypass the microbial formation step and must not be used as evidence of the plasma concentrations attained after ordinary dietary precursor intake [97,98].

Quantitative dietary intervention studies offer useful comparators. After ingestion of cocoa containing 19.8 or 68.3 mg of flavan-3-ols, the plasma Cmax of a hydroxyphenyl-γ-valerolactone sulfate was 1.150 ± 0.742 and 1.384 ± 0.648 µmol/L, respectively; corresponding free metabolite concentrations were substantially lower. After administration of 100 mg of daidzein in soymilk to 12 equol-producing women, the reported mean Cmax for total equol was 89 ± 78 nmol/L, with equol mainly present as a 7-O-glucuronide [94,99]. These results cannot be extrapolated indiscriminately to non-producers, different food matrices or chronic exposure.

Direct oral supplementation with purified urolithin A produces a different exposure scenario from an ellagitannin-rich diet. In a randomised trial involving 1000 mg/day over four months, the reported plasma concentration at the four-month visit was 1038 pg/mL (equivalent to 1.038 ng/mL) for unconjugated urolithin A, compared with 1014 ng/mL for urolithin A glucuronide [98]. The difference in chemical form and mass concentration is substantial, and neither observation should be labelled Cmax. The trial found improvements in selected secondary muscle-endurance outcomes, without significant between-group differences in its primary 6 min walk-distance and maximal ATP-production endpoints. These results do not establish a therapeutic indication or the efficacy of a dietary precursor intervention.

Quantitative comparison is now possible for two illustrative metabolite–mechanism pairs, although the relevant studies do not share a common dose or sampling design. For urolithin A, 50 µmol/L of free compound was used in HT29 epithelial cell experiments examining the AhR–Nrf2 axis [56], whereas the free plasma concentration after direct supplementation reported at four months was approximately 0.0045 µmol/L (calculated from 1.038 ng/mL using a molecular mass of approximately 228.2 g/mol) [98]. The nominal cell-culture concentration is about 11,000 times higher, but this is not a tissue exposure ratio or an IC50 comparison. For equol, PPARγ reporter assays employed approximately 10–20 µmol/L free equol [68], compared with a total-plasma-equol Cmax of 0.089 ± 0.078 µmol/L, predominantly as glucuronide, after daidzein-containing soymilk in confirmed producers [99]. Because unbound intracellular concentrations, conjugate bioactivity and the timing of exposure were not matched, these differences indicate an evidence gap rather than prove an absence of biological effect. Table 6 separates the measured forms and experimental comparators.

Additional comparisons require matching the relevant tissue compartment. For example, activated human leukocytes exposed ex vivo to free urolithins at 1–15 µmol/L showed altered eicosanoid profiles, while tested conjugates were inactive; these concentrations were discussed in relation to colonic rather than circulating exposure [64]. Estimates from urinary sulforaphane metabolites likewise depend on whether plant myrosinase is present in the intervention [37,38]. Pharmacokinetic interpretation should therefore specify com-

partment, sampling schedule, dose, metabolic conjugation and analytical method rather than compare unrelated nominal concentrations.

Table 6. Selected human metabolite exposures and experimental comparators. Measurements relate to different interventions, chemical species and sampling schedules; the table does not provide a pooled pharmacokinetic range or establish in vivo target engagement. Abbreviations: AhR, aryl hydrocarbon receptor; Cmax, maximum plasma concentration; HT29, human colorectal adenocarcinoma cell line; NR, not reported; Nrf2, nuclear factor erythroid 2-related factor 2; PPARγ, peroxisome proliferator-activated receptor gamma; tmax, time to maximum concentration; UA, urolithin A.

Metabolite/Exposure	Human Intervention	Measured Form and Matrix	Quantitative Observation	Comparison/Limitation	Primary Study
Urolithin A	250/1000 mg pomegranate extract	UA conjugates and free UA, plasma	Conjugates detectable ≈8 h post-dose; unconjugated UA in few subjects; Cmax NR	No matched target-engagement study in this row. Note: free versus conjugated urolithin A is not specified by a common concentration metric; do not substitute total levels for free exposure.	[93]
S-equol	100 mg daidzein in soymilk; 12 equol-producers	Total equol, mainly equol-7-glucuronide, plasma	Mean Cmax 89 ± 78 nmol/L; tmax 36 ± 10 h	Free equol activated PPARγ reporter at 10–20 µmol/L in 3T3-L1 cells [68], compared with total plasma Cmax ≈ 0.089 µmol/L, predominantly glucuronide [99]; different chemical species and interventions.	[68,95,99]
Phenyl-γ-valerolactone sulfate	Conventional cocoa vs. flavanol-rich cocoa	Hydroxyphenyl-γ-valerolactone sulfate, plasma	Cmax 1.150 ± 0.742 vs. 1.384 ± 0.648 µmol/L	Circulating sulfate cannot be compared directly with free valerolactones used in cellular assays; chemically matched experimental concentrations were not verified in this comparison.	[94]
Urolithin A, direct supplement	1000 mg/day purified UA for 4 months	Free UA and UA glucuronide, plasma	Four-month plasma levels: free UA 1038 pg/mL (=1.038 ng/mL; ≈0.0045 µmol/L); UA glucuronide 1014 ng/mL. These are not Cmax values.	HT29 AhR/Nrf2/barrier experiments used free UA at 50 µmol/L [56], ≈11,000-fold above this free plasma concentration [98]. Different dosing, sampling, matrix and exposure; not proof of lack of efficacy.	[56,63,96,98]
Sulforaphane/glucoraphanin	Randomised crossover human study ($n = 16$), broccoli-seed extract with vs. without mustard-seed myrosinase	Urinary sulforaphane-derived metabolites; estimated conversion, not free plasma Cmax	39.8 ± 3.1% with added myrosinase vs. 18.6 ± 3.1% without	Formulation-dependent exposure; plant and microbial enzymatic contributions cannot be conflated	[38]

3. Discussion

3.1. Microbial Biotransformation as the Link Between Dietary Phytochemicals and Host Health

The evidence synthesised in this narrative review highlights microbial biotransformation as a fundamental mechanism linking dietary phytochemicals with host physiology. While phytochemicals have traditionally been investigated based on their intrinsic chemical properties and direct biological activities, increasing evidence indicates that microbial metabolites, rather than the parent compounds themselves, may contribute to some biological responses following phytochemical consumption [12,19,20,72]. Consequently, the gut micrsobiota should be regarded as an active metabolic organ that expands the functional diversity of dietary phytochemicals and shapes their biological activity after ingestion.

This concept represents an important shift in phytochemical research. Instead of viewing dietary phytochemicals as isolated bioactive molecules, they should increasingly be considered substrates for a dynamic host–microbiota metabolic network. Through enzymatic reactions such as deglycosylation, hydrolysis, demethylation, dehydroxylation, reduction, and ring cleavage, gut microorganisms convert structurally diverse phytochemicals into metabolites with distinct physicochemical characteristics, which can display absorption, distribution, and biological activity profiles that differ from those of their precursors [8,12,16]. These observations suggest that microbial metabolism should not be regarded merely as a determinant of phytochemical absorption but as a critical process governing their physiological relevance.

An important implication emerging from the available evidence is that the health effects associated with phytochemical-rich diets cannot be explained solely by the concentration or diversity of phytochemicals present in foods. Instead, biological responses appear to result from the interaction between dietary composition, food matrix characteristics, microbial metabolic capacity, and host physiology. Plant foods contain complex mixtures of phytochemicals that undergo simultaneous microbial metabolism, generating diverse metabolite profiles that are unlikely to be predicted from the behaviour of individual compounds alone. Consequently, studying isolated phytochemicals provides only a partial understanding of the biological effects associated with habitual dietary patterns, reinforcing the importance of investigating whole foods and dietary patterns within the context of host–microbiota interactions [100–102].

Despite the remarkable structural diversity of dietary phytochemicals, the evidence reviewed also suggests a notable functional convergence following microbial biotransformation. Chemically distinct compounds are transformed into metabolites that regulate common physiological processes, including intestinal homeostasis, immune function, oxidative stress, inflammatory signalling, energy metabolism, and inter-organ communication. This convergence suggests a testable mechanistic hypothesis, but it cannot by itself establish that specific microbial metabolites account for the health outcomes associated with distinct dietary patterns [21,22,25,102]. Rather than acting through isolated mechanisms, microbial metabolites appear to participate in interconnected signalling networks that coordinate multiple physiological responses.

Collectively, these findings support a transition from a compound-centred perspective towards a systems biology framework in which the biological activity of dietary phytochemicals is understood as the integrated outcome of interactions among food composition, microbial metabolism, and host molecular signalling. This conceptual framework helps generate hypotheses about the health effects of phytochemical-rich diets and highlights microbial biotransformation as one determinant of interindividual variability and an essential component of precision nutrition strategies [12,16,72,92].

3.2. Interindividual Variability and Emerging Systems Biology Approaches

One of the most important challenges emerging from current research is the considerable interindividual variability in microbial phytochemical metabolism. Although individuals may consume similar amounts of phytochemical-rich foods, differences in gut microbiota composition, microbial gene content, enzymatic capacity, host genetics, lifestyle, age, medication use, and dietary habits can lead to markedly different metabolite profiles and biological responses [16,19,72]. Consequently, the health benefits associated with dietary phytochemicals are increasingly recognised as being influenced not only by dietary intake but also by the metabolic competence of the gut microbiota.

The relevance of microbial metabotypes to clinical heterogeneity has some direct human support: in a randomised pomegranate-extract intervention, cardiovascular biomarker

responses differed across urolithin-producing phenotypes, although attribution to a specific circulating urolithin remains unresolved [88].

This variability has given rise to the concept of microbial metabotypes, whereby individuals are classified according to their capacity to generate specific microbial metabolites from dietary substrates. Established examples of variable microbial metabolite production include urolithins from ellagitannins and equol from daidzein; further pathways, including the formation of norathyriol from mangiferin, require more detailed functional and clinical characterisation [8,16,91,103].

The existence of distinct metabotypes provides a plausible explanation for the heterogeneous responses frequently observed in nutritional intervention studies and may contribute to the inconsistent associations reported between phytochemical intake and clinical outcomes.

Despite significant progress in identifying microbial metabolites, the microbial and enzymatic mechanisms responsible for many biotransformation pathways remain incompletely understood. For numerous phytochemicals, microbial conversion can be demonstrated experimentally, yet the specific microbial taxa, genes, and enzymes involved have not been fully characterised. This "black-box" nature of microbial metabolism continues to represent one of the major limitations of the field and restricts the mechanistic interpretation of host–microbiota interactions [12,16]. Furthermore, many biologically relevant metabolites are likely to remain unidentified, highlighting the complexity of the gut metabolome and the need for more comprehensive analytical approaches.

Addressing these challenges requires analytical strategies capable of integrating microbial composition with functional activity and host responses. Recent advances in metagenomics, metatranscriptomics, metaproteomics, metabolomics, and computational biology have substantially expanded current understanding of microbial phytochemical metabolism by enabling the simultaneous characterisation of microbial communities, expressed genes, enzymatic pathways, and circulating metabolites [12,72]. When combined with suitable experimental designs, these technologies can provide functional information beyond microbial taxonomy and help characterise metabolic networks in relation to host outcomes.

The integration of multi-omics data through systems biology and artificial intelligence is expected to further transform phytochemical research. Machine learning algorithms, network-based analyses, and predictive metabolic models are increasingly being used to identify microbial biomarkers, predict metabolite production, reconstruct microbial metabolic pathways, and explore complex interactions between diet, microbiota, and host physiology. These approaches have the potential to improve the reproducibility of microbiome research and facilitate the development of personalised nutritional interventions based on an individual's microbial metabolic capacity [12,72,92].

Taken together, these findings indicate that interindividual variability is not simply a source of experimental heterogeneity but rather a fundamental biological characteristic of microbial phytochemical metabolism. A more comprehensive understanding of microbial metabotypes and the integration of multi-omics technologies may support the identification and validation of predictive biomarkers of dietary response, clarifying the mechanisms underlying phytochemical bioactivity and advancing microbiome-informed precision nutrition.

3.3. Current Challenges, Limitations, and Future Perspectives

Despite the considerable progress made in elucidating the interactions between dietary phytochemicals, the gut microbiota, and host physiology, several scientific and methodological challenges continue to limit translation into evidence-based nutritional and clinical applications. One of the major challenges is the substantial heterogeneity among available

studies with respect to experimental models, dietary interventions, analytical methodologies, microbiome profiling techniques, metabolomic platforms, and outcome measures. This methodological diversity hampers comparisons across studies and complicates the establishment of robust causal relationships between microbial biotransformation and health outcomes [19,20,72].

Although urolithins and selected phenolic catabolites have well-characterised biosynthetic steps, genes and enzyme activities remain incompletely mapped for many other dietary compounds [12,51]. A separate challenge is establishing whether measured metabolite concentrations and chemical forms are compatible with the experimental concentrations that modulate target pathways; the quantitative examples in Table 6 illustrate the importance of distinguishing free metabolites from host conjugates [56,68,98,99]. Whole-food matrices and dietary patterns complicate causal attribution, since microbial responses to fibre and other substrates may accompany phytochemical-specific transformations [101,102]. Future studies should integrate enzyme-level evidence, analytically characterised human exposure and clinically meaningful outcomes.

The current body of evidence is also constrained by the predominance of in vitro experiments, animal models, and short-term intervention studies. Although these approaches have generated valuable mechanistic insights, they cannot fully reproduce the complexity of long-term human host–microbiota interactions or the adaptive changes associated with habitual dietary patterns. Consequently, well-designed longitudinal human studies integrating dietary assessment, microbiome composition, microbial function, metabolomic profiling, and clinical outcomes are needed to investigate causal relationships and determine the long-term physiological relevance of microbial phytochemical metabolism [72,92].

This narrative review integrates experimental, pharmacokinetic and human evidence but does not constitute an exhaustive systematic review or provide a formal certainty-of-evidence assessment. Differences in substrates, microbial strains, analytical methods, tested molecular forms and outcomes limit direct comparison across studies. The review was conducted as a single narrative synthesis, with the available literature considered up to 31 October 2026; there was no separately designed post-peer-review search update. The archived Rayyan project supports numerical reporting of the original title-and-abstract screening and subsequent full-text reading. However, complete database-specific search histories, a database-by-database record of the later literature identified through citation tracing, and a coded record of the thematic prioritisation from 322 to 173 publications are unavailable. The surviving January 2026 search log is partial and does not permit reconstruction of a full reproducible three-database search strategy. Accordingly, the 173-item Mendeley collection and the references ultimately cited in this article are a curated drafting resource and a bibliography, respectively, not final counts arising from a formal, separately coded eligibility stage. The principal challenges and research priorities are summarised in Table 7.

Building upon these priorities, future research should focus on the standardisation of analytical methodologies for phytochemical characterisation, microbiome profiling, and metabolite identification to improve reproducibility and facilitate comparisons across studies. Greater efforts are also required to identify the microbial taxa and enzymes responsible for specific biotransformation pathways, characterise previously unknown microbial metabolites, and clarify the molecular mechanisms through which these metabolites influence host physiology. The integration of metagenomics, metatranscriptomics, metaproteomics, metabolomics, and computational modelling will be instrumental in reconstructing microbial metabolic networks and identifying predictive biomarkers of individual dietary responses [12,72].

Table 7. Current knowledge, research challenges and future priorities in phytochemical–microbiota research. Abbreviation: Evidence statements are descriptive summaries, not formal certainty-of-evidence ratings. The distinction between phytochemical catabolites, host conjugates and other microbial products applies throughout. Representative literature includes [1,12–14,16,19,23,32,85,93,98].

Research Area	Current Knowledge	Key Challenges	Future Priorities
Microbial biotransformation	Defined gut microbial reactions can yield metabolites with physicochemical and biological properties distinct from those of their parent compounds; increased systemic exposure or potency is compound- and form-dependent, not universal.	Many microbial enzymes, genes, and metabolic pathways remain unidentified.	Functional characterisation of microbial enzymes through integrated multi-omics and systems biology approaches.
Interindividual variability	Microbial capacity to produce selected catabolites differs between individuals; the relevance of these differences to clinical responses remains incompletely validated.	Limited understanding of responder and non-responder phenotypes and their clinical implications.	Identification of predictive microbial biomarkers to support precision nutrition.
Food matrix and dietary patterns	Phytochemicals are consumed within complex food matrices containing multiple interacting bioactive compounds.	Synergistic and antagonistic interactions among phytochemicals remain poorly characterised.	Greater emphasis on whole-food and dietary pattern interventions rather than isolated compounds.
Experimental evidence	Experimental studies have identified numerous microbial metabolites and mechanistic pathways.	Most evidence originates from in vitro models, animal studies, or short-term interventions.	Large multicentre longitudinal human studies integrating dietary, microbiome, metabolome, and clinical data.
Analytical methodologies	Advances in metabolomics have expanded the identification of gut-derived metabolites.	Lack of standardised analytical workflows and metabolite annotation limits comparability across studies.	Harmonised analytical protocols, shared databases, and validated metabolite libraries.
Dose–response relationships	Associations between microbial metabolites and health outcomes are increasingly recognised.	Quantitative relationships between metabolite concentrations and biological effects remain poorly defined.	Pharmacokinetic studies and exposure–response analyses to establish biologically relevant thresholds.
Multi-omics integration	Multi-omics approaches provide functional insights into host–microbiota interactions.	Functional datasets are rarely integrated within the same investigation.	Integration of metagenomics, metatranscriptomics, metaproteomics, metabolomics, and artificial intelligence.
Clinical translation	Selected compounds show preclinical activity and some have early human intervention data, but clinical efficacy for most metabolites remains unestablished.	Limited translation into clinical guidelines and personalised nutritional recommendations.	Development of microbiome-informed precision nutrition strategies, microbiome-targeted therapies, and next-generation functional foods.

Further progress will require coordinated work across phytochemistry, microbial enzymology, nutrition, analytical pharmacology and clinical investigation. Strain-resolved functional assays can identify reactions that are otherwise obscured by genus-level associations, while targeted metabolomics can distinguish free catabolites from glucuronide or sulfate conjugates. Subsequent human studies should predefine the precursor dose, chemical form, microbial metabotype, safety measures and clinical endpoints. This approach may support the evaluation of pharmacological leads, exposure biomarkers and precision nutrition strategies without assuming that experimental pathway changes establish human therapeutic efficacy [12,16,51,93,98].

3.4. Translational and Therapeutic Perspectives

Potential applications of phytochemical-derived microbial metabolites should be distinguished by their level of translational maturity. A chemically defined metabolite may be evaluated as a pharmacological lead or as a directly administered intervention, as in studies of urolithin A. Alternatively, microbial producer phenotypes and conjugated-metabolite profiles may be investigated as biomarkers of exposure or response. A third approach targets microbial enzymes or producing organisms, although strain carriage and community context affect whether a desired catabolite is formed in vivo [44,45,51]. Such approaches require explicit verification of substrate provenance and cannot be inferred from broad shifts in microbiome composition.

Potential biomarker and therapeutic applications should remain distinct. Urinary phenyl-γ-valerolactone conjugates have been evaluated as dietary flavan-3-ol intake biomarkers in human studies [55], whereas trials of purified urolithin A test a pharmacological exposure that bypasses microbial precursor conversion [89]. These investigations should not be combined to infer efficacy of phytochemical-rich dietary patterns.

Proof of concept is most developed for selected urolithin A interventions. A randomised study of direct supplementation in older adults reported improvements in secondary muscle-endurance outcomes but not significant differences for the prespecified primary functional and bioenergetic endpoints; it therefore supports further trials rather than established therapeutic efficacy [98]. A recent preclinical study of a mouse model of heart failure with preserved ejection fraction connected urolithin A dosing to AMPK–mTOR–ULK1-associated mitophagy and reduced remodelling, but this cannot be transferred directly to clinical treatment recommendations [66].

Translation requires resolving major formulation and dose-standardisation problems. Food processing alters plant myrosinase activity and precursor release; the food matrix may change intestinal delivery; microbial producer status varies; and purified oral metabolites bypass the need for microbial formation. Phase-II conjugation, possible local deconjugation, chemical stability, oral bioavailability, drug–metabolite interactions and the feasibility of achieving active unbound tissue concentrations require independent investigation. A compound's activity in a cell model is insufficient to justify a therapeutic indication [93,99].

Future studies should specify whether the intervention involves a food, characterised extract, purified microbial metabolite, or microbiome manipulation. Key requirements include human exposure–response measurements of both free and conjugated species, assessment of formulation and stability, interaction and safety surveillance, microbial-metabotype stratification, and clinically relevant, prospectively defined endpoints. Stable-isotope tracing, targeted mass spectrometry, strain-resolved genomics and enzyme assays may help establish causal links between precursor intake, microbial reaction, metabolite availability and target-organ effects. These steps would separate compounds that are experimentally active from those with convincing potential for practical nutritional or therapeutic applications.

4. Materials and Methods

4.1. Review Design

This manuscript was prepared as a narrative review supported by a structured literature search to critically examine the microbial biotransformation of dietary phytochemicals and the formation, biological activity, and translational relevance of gut-derived metabolites. The review integrated evidence from phytochemistry, microbiology, metabolomics, molecular pharmacology, and nutritional sciences, with particular emphasis on identifying direct evidence of metabolite formation and distinguishing it from downstream biological associations. Evidence from in vitro experiments, ex vivo fermentation models, animal

studies, and human observational and intervention studies was considered to provide a multidisciplinary understanding of the mechanisms underlying microbiota-mediated phytochemical metabolism and their potential implications for human health.

4.2. Literature Search

This work was conducted as one narrative review, supported by literature searches in PubMed/MEDLINE, Scopus and Web of Science and identification of additional pertinent original studies through reference-list checking. The search and literature identification process began in January 2026, with initial database screening documented through May 2026; relevant literature was considered through 31 October 2026 within the same review process. There was no separate, protocol-defined literature update conducted after the peer-review decision. The surviving partial search log dated 15 January 2026 records selected PubMed/MEDLINE and Web of Science combinations of gut–brain-axis or psychobiotic terms with phytochemical classes and plant-derived compounds. The team confirmed that Scopus was also searched, although complete database-specific strategies, exported search histories and exact calendar dates of the final searches were not retained. As the review developed, its thematic focus broadened from gut–brain-axis mechanisms to the chemistry, microbial enzymology, pharmacokinetics and translational relevance of phytochemical-derived metabolites. Additional pertinent original research was identified by examining citations in selected publications, including studies of microbial conversion, experimental signalling and human exposure. The 913 records reported in Section 4.3 describe the set imported into Rayyan for documented screening and should not be interpreted as an exhaustive yield for every subsequently consulted publication. Mendeley was used for reference management.

4.3. Literature Selection

Study selection was based on relevance to the review objectives, prioritising original studies investigating dietary phytochemicals, microbial biotransformation, metabolite formation, molecular mechanisms, pharmacokinetics, and physiological effects. Publications outside the thematic scope, probiotic-only studies, and studies involving poorly characterised plant extracts were excluded. Review articles were used for background information and reference identification but were not considered primary mechanistic evidence. A total of 913 records were imported into Rayyan. After removing 31 duplicates, three reviewers independently screened the titles and abstracts of 882 records, resolving disagreements through consensus. Of these, 560 were excluded, and 322 publications were retained for full-text assessment. Subsequently, 173 references considered most relevant to the review objectives were organised in Mendeley and distributed among the co-authors for thematic analysis and manuscript preparation. Two additional co-authors contributed to the evaluation of assigned sections and the narrative synthesis. The selection of references for the final manuscript was based on their relevance to the scientific topics discussed, without a separate formal quality-ranking procedure.

4.4. Data Extraction and Evidence Synthesis

Following study selection, co-authors independently examined the full-text articles relevant to their assigned thematic areas. Information on phytochemical characteristics, microbial taxa and enzymes, biotransformation pathways, metabolites, molecular targets, pharmacokinetics, and physiological outcomes was extracted and synthesised narratively. Evidence was critically interpreted according to the experimental models and mechanisms reported, distinguishing direct microbial biotransformation from broader microbiota-associated effects and preclinical findings from human evidence. No standardised extraction form,

formal risk-of-bias assessment, or quantitative meta-analysis was performed. ChatGPT (OpenAI, GPT-6.2) was used to create the conceptual illustrations in Figures 2 and 3. The authors verified the scientific information and retained responsibility for the accuracy and presentation of both figures.

5. Conclusions

Gut microorganisms can convert selected dietary phytochemicals into structurally distinct metabolites through pathways involving substrate-specific enzymes and, frequently, cooperation between bacterial species. Evidence is particularly compelling for the formation of urolithins, S-equol, enterolignans and certain phenyl-γ-valerolactones. Directly demonstrated biotransformation should be distinguished from changes in broader microbial metabolism following dietary interventions.

Experimental studies link several characterised metabolites to Nrf2, NF-κB, AMPK and related signalling networks, but these findings depend on chemical form, dose and model. Human pharmacokinetic studies show pronounced interindividual variability and frequent predominance of glucuronide or sulfate conjugates; free-metabolite exposure and clinical target engagement often remain insufficiently defined. Future work should combine strain-resolved enzymology, targeted exposure measurements and well-controlled clinical trials before therapeutic claims or personalised recommendations can be substantiated.

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Conflicts of Interest: P.R. is a Guest Editor on this Collection, but was not involved in the evaluation of this work. The remaining authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

AhR	Aryl hydrocarbon receptor
AMPK	AMP-activated protein kinase
MAPK	Mitogen-activated protein kinase
NF-κB	Nuclear factor kappa B
Nrf2	Nuclear factor erythroid 2-related factor 2
O-DMA	O-Desmethylangolensin
PI3K/Akt	Phosphoinositide 3-kinase/protein kinase B
PPARγ	Peroxisome proliferator-activated receptor gamma

SCFAs	Short-chain fatty acids
SIRT1	Sirtuin 1
TLRs	Toll-like receptors

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