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REVIEW ARTICLE

Medicinal Plants and the Gastrointestinal Microbiota in Chronic Diseases Modulation: A Structured Mechanistic and Translational Review

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Abstract

The gut microbiome supports digestion, immunity, and metabolism; its imbalance (dysbiosis) drives inflammation and metabolic dysfunction, contributing to chronic diseases such as diabetes, cardiovascular disease, inflammatory bowel disease, and autoimmune disorders. Medicinal plants provide a wide range of phytochemicals (such as polyphenols, flavonoids, alkaloids, saponins), which reach the colon and undergo two-sided interactions with microbes in the gut, acting as potential microbiome modulators and substrates of biotransformation into bioactive metabolites. This structured narrative review synthesises evidence from peer-reviewed studies indexed in PubMed, Scopus, and Web of Science over the last 10 years on the role of medicinal plants in microbiome-mediated chronic disease modulation. This literature is organised into three mechanistic axes: (i) perturbations, defined here as measurable shifts in microbial diversity or taxonomic composition relative to a baseline or healthy reference state, together with beneficial taxa enrichment; (ii) alterations in microbial metabolite output, especially short-chain fatty acids (SCFAs) and other immunometabolic mediators; and (iii) downstream host metabolic and immune signalling. Rather than broad descriptive summaries, the literature is organised using an axis-based mechanistic framework, highlighting key translational constraints such as botanical heterogeneity, dose/formulation variability, and inconsistent microbiome endpoint standardisation, that must be addressed to strengthen human evidence and clinical relevance. Illustrative microbiome-mediated processes involve botanicals such as turmeric (curcumin), ginseng (ginsenosides), and green tea (catechins), though evidence strength varies by study design. Future progress requires standardised phytochemical characterisation, microbiome-stratified trials, and integration of multi-omics

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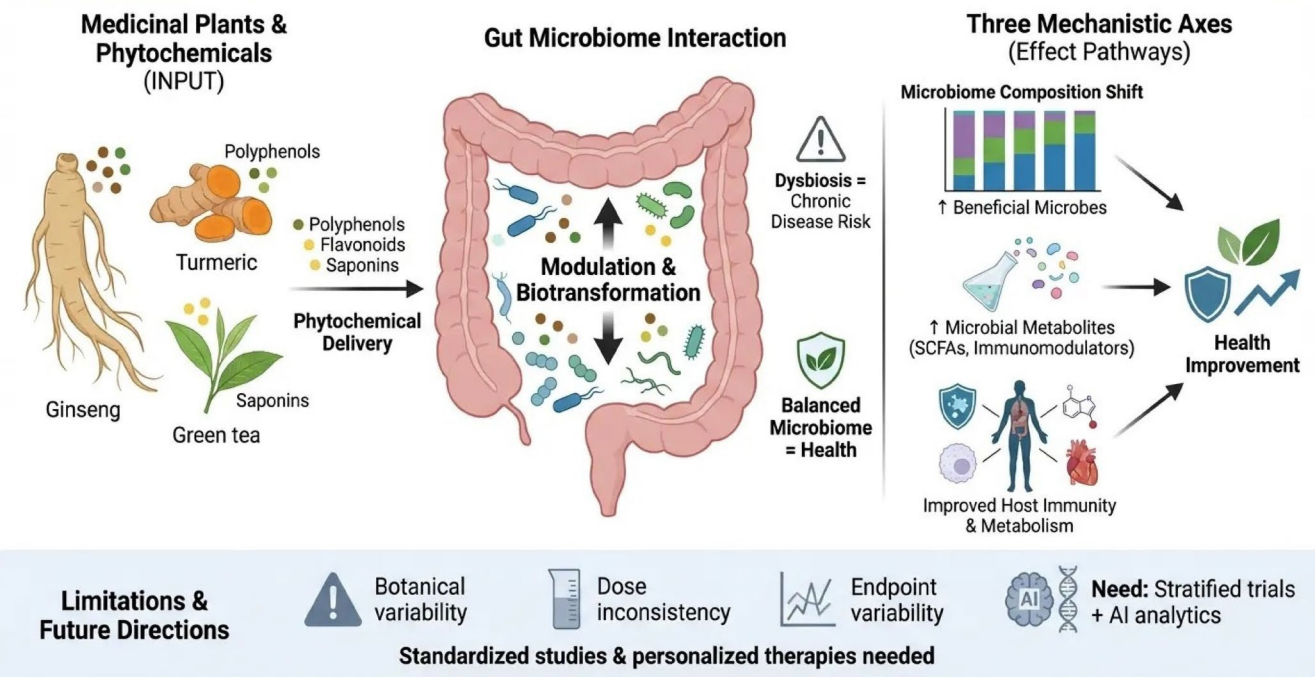
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with artificial intelligence analytics to enhance mechanistic insight, identify responders, and enable personalised plant-based microbiome therapies.

Graphical Abstract



Introduction

The global burden of chronic diseases, like diabetes, cardiovascular diseases, inflammatory bowel disease, and autoimmune disorders, continues to rise, posing significant public health challenges. These conditions are often multifactorial, involving genetic, environmental, and lifestyle influences [1]. The gut microbiota, an intricate community containing trillions of microorganisms living in the human gastrointestinal tract, has become a critical factor in human health. Its influence extends beyond digestion to modulating immunity, metabolic functions, and even neurobehavioral health [2]. In this review, "gut microbiota" denotes the microbial community in the gastrointestinal tract, while "gut microbiome" encompasses the microorganisms, their genes, and their combined functional activities. Dysbiosis, or microbial imbalance, is increasingly connected to the emergence and advancement of chronic disorders like diabetes, cardiovascular diseases, inflammatory bowel disease (IBD), and certain cancers [2].

Interestingly, medicinal plants have been revered for decades for their therapeutic properties. From traditional systems like Ayurveda and Traditional Chinese Medicine to modern pharmacology, medicinal plants have provided a plethora of bioactive compounds with significant health benefits [3, 4]. Medicinal plants contain bioactive compounds such as polyphenols, flavonoids, and alkaloids that can interact with gut microbes and may influence microbial composition and activity. These interactions may generate bioactive metabolites that are associated with inflammatory, metabolic, and immune-regulatory pathways [5]. The gastrointestinal microbiota's emerging role as a therapeutic focus amplifies the relevance of these findings. Integrating medicinal plants and microbiome research could transform chronic disease treatment by offering cost-effective, natural, and sustainable therapeutic options. In addition, medicinal plants are attracting increasing attention for their potential to modulate gut microbiota. The convergence of these two fields, medicinal plants and gut microbiome research, offers a promising avenue for managing chronic diseases. Recent research highlights a potential synergy between medicinal plants and the gut microbiota, unveiling novel pathways for treating chronic disorders [6, 7].

However, limited mechanistic understanding of the interaction between medicinal plants and the gastrointestinal microbiome has constrained their integration into modern therapeutic strategies for chronic disease management. To address this gap, this review examines this relationship and its implications for chronic disease management. Accordingly, this review explores gut microbiota mediated processes through which medicinal plants and important phytochemicals can regulate chronic diseases

biology. Specifically, we focus on three mechanistic axes: the changes in microbial diversity and taxonomic composition, changes in microbial metabolites (such as SCFAs and related immunometabolic mediators), and downstream host metabolic and immune signaling. We do not attempt a broad ethnobotanical catalog, nor a full pharmacognosy or clinical guideline review; instead, we prioritise mechanistic plausibility and translational considerations relevant to chronic disease prevention and adjunct therapy.

While previous reviews have described interactions between medicinal plants and the gut microbiome in broad or compound-specific terms [6, 7], the present review differs by organising this evidence into a structured, axis-based mechanistic framework linking (i) microbial taxa, (ii) microbial metabolites, and (iii) host signaling pathways. In addition, this review integrates translational considerations, including botanical heterogeneity, microbiome variability, and methodological constraints, thereby providing a more application-oriented synthesis of the field. As a result, this study will: (1) summarise the main evidence to support the association between medicinal plants and microbiome structure and function; (2) outline the connection between the microbial changes that are associated with plants, their production of metabolites, and their pathways related to chronic diseases; and (3) identify the methodological priorities for future translational studies. Accordingly, the novelty of this review lies not in identifying new individual mechanisms, but in integrating existing evidence into a structured, multi-level framework that connects mechanistic insight with translational relevance.

To visually describe the bidirectional communication between the gut microbiome and medicinal plants, we present a mechanistic model, which links plant-derived phytochemicals with the process of microbiome restructuring, microbial biotransformation, and host-signaling cascade responses that mediate chronic disease regulation. Figure 1 synthesises the central conceptual argument of this review by showing that medicinal plants do not act only at the level of phytochemical exposure, but through a layered interaction involving microbial restructuring, microbial biotransformation, and downstream host signaling. This integrative view supports the manuscript's three-axis framework by linking plant-derived substrates to taxonomic shifts, metabolite generation, and host inflammatory, metabolic, and immune pathways. It also clarifies why microbiome-mediated effects should be interpreted as a network of interactions rather than a single linear mechanism. Most plant-microbiome studies are heterogeneous in terms of cohort, formulations and pipelines. In observational studies, microbial community changes are to be regarded as the correlational but not causal determinants of disease phenotypes. There is strong mechanistic inference when research

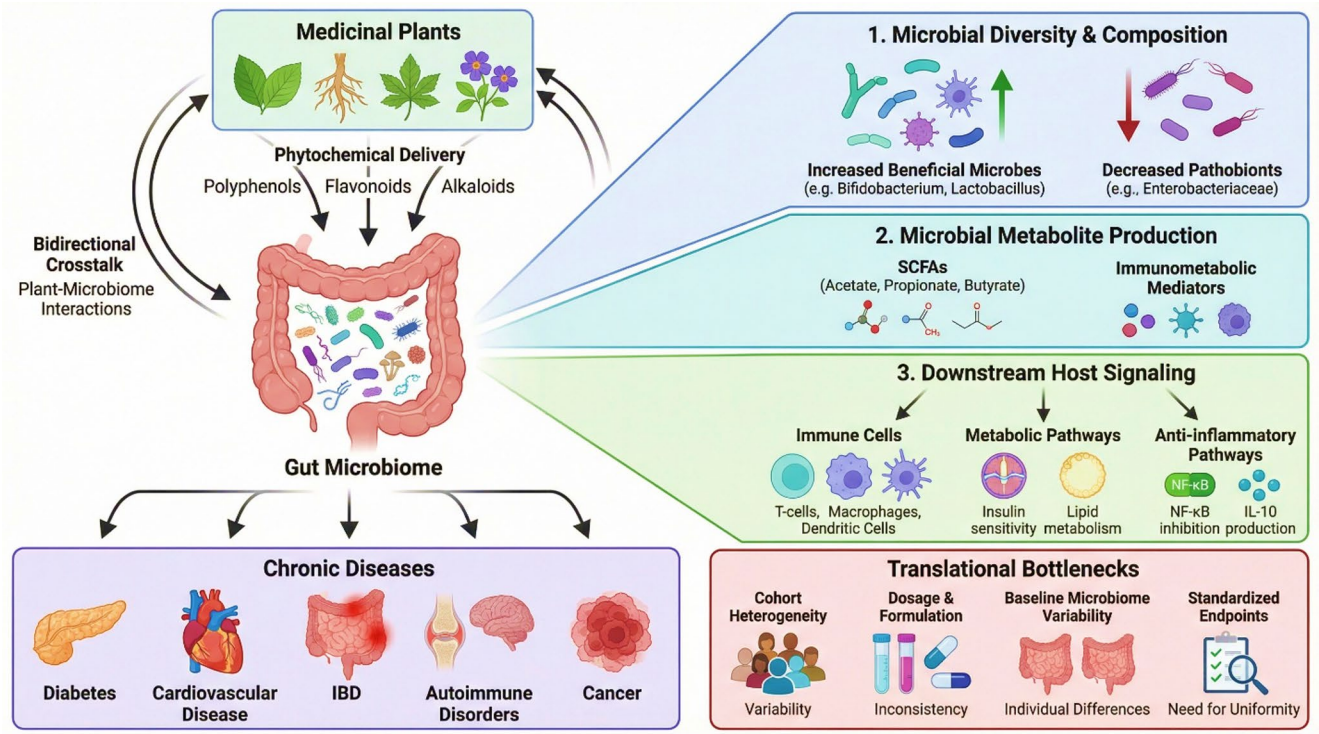


Fig. 1 Mechanistic model summarising the interplay between medicinal plants, gut microbiome, and chronic disease regulation: bioactive phytochemicals from medicinal plants influence microbial diversity and metabolite production, leading to downstream modulation of host immune, metabolic, and inflammatory pathways, offering promising natural strategies for chronic disease management

has determined temporality, dose response relationships and functional readouts, such as metabolite profiles or markers of functional barriers and/or microbiome-targeted experimental perturbations (for example, antibiotic perturbation or germ-free and colonization models).

Methodology

Study Design

This review was conducted as a structured narrative synthesis aimed at integrating mechanistic and translational evidence on interactions between medicinal plants, the gut microbiome, and chronic disease pathways. While a targeted database search was performed to ensure broad coverage, the review was not designed as a systematic review, and therefore did not follow formal systematic review protocols (e.g., PRISMA).

Search Strategy

A targeted literature search was conducted in PubMed, Scopus, and Web of Science (final search date: 6 April 2026). Search terms were developed across three concept domains: (i) medicinal plants/phytochemicals, (ii) gut microbiome, and (iii) chronic disease/dysbiosis. The search strategy was intended to identify representative and mechanistically informative studies, rather than to exhaustively capture all eligible literature. Key terms used were: medicinal plant, phytochemical, polyphenol, flavonoid, alkaloid, herbal medicine, gut microbiome, microbiota, dysbiosis, chronic disease, diabetes, metabolic syndrome, cardiovascular, inflammatory bowel disease. In addition, reference lists of included papers and relevant reviews were hand-screened to identify additional eligible studies.

Study Selection Approach

Studies were selected based on relevance to the manuscript's mechanistic framework, translational relevance, and the presence of microbiome-related outcomes linked to host metabolic, immune, or inflammatory pathways. Study identification and selection were conducted independently by at least two authors, who screened titles, abstracts, and full-text articles for relevance to the mechanistic framework and translational focus of the review. Any discrepancies in study inclusion or interpretation were resolved through discussion and consensus among the authors. Although this review did not follow a formal systematic screening protocol, this approach was used to improve consistency and reduce potential selection bias.

Data Extraction, Evidence Organisation and Synthesis

Due to heterogeneity in study designs, botanical interventions, and microbiome endpoints, findings were synthesised narratively. Evidence was organised into three recurring mechanistic axes:

(i) shifts in microbial diversity and beneficial taxa;
(ii) modulation of microbial metabolites (including SCFAs and related immunometabolic mediators); and.
(iii) downstream host metabolic/immune pathway changes relevant to chronic disease phenotypes.

Subsequently, gaps in the current studies were recognised. The study's findings were organised thematically to improve readability and coherence. To reduce overinterpretation, mechanistic claims were interpreted according to evidence level (clinical, observational, animal, in vitro) and are discussed with explicit attention to translational limitations (botanical heterogeneity, interindividual microbiome variability, and trial design constraints). We use "associated with" for observational findings and reserve causal language for interventional or mechanistic studies with appropriate controls.

This approach aligns with best practices for narrative reviews, where literature identification supports conceptual synthesis rather than quantitative aggregation or formal evidence grading [8].

To improve interpretive clarity, each figure was designed as a visual synthesis of a distinct analytical level of the manuscript, including overarching mechanism, host-functional consequences, disease-pathway context, disease-cluster translation, and implementation barriers.

Evidence Grading and Critical Appraisal Approach

Because this article is a structured narrative review rather than a formal systematic review, we did not perform a risk-of-bias assessment using standardised systematic review tools. However, to improve interpretive rigor, the evidence was appraised according to study design and translational strength. Included evidence was categorised as Level 1, human randomised controlled trials or controlled clinical interventions; Level 2, human observational studies; Level 3, animal studies; and Level 4, in vitro or ex vivo mechanistic studies. Within each category, interpretation additionally considered sample size and representativeness, risk of confounding from diet, medication use, geography, baseline microbiome composition, and disease heterogeneity, as well as reproducibility and consistency across studies. Methodological heterogeneity, including botanical

characterisation, dose and formulation, duration, sequencing platform, bioinformatic pipeline, and microbiome endpoints, was also taken into account. Findings from smaller, heterogeneous, or predominantly preclinical studies were therefore described cautiously, whereas stronger language was reserved for better-supported human evidence. While formal risk-of-bias tools were not applied, the multi-author selection process and consensus-based inclusion were used to improve interpretive reliability.

Figure Preparation and Validation

All schematic figures presented in this review (Graphical Abstract, Figs. 1, 2, 3, 4 and 5) were created using BioRender (https://BioRender.com). All graphical elements, including microbial taxa, gastrointestinal anatomical structures, and molecular signaling pathways, were manually curated based on evidence synthesised from peer-reviewed sources cited in this manuscript. Taxonomic labels and pathway components were cross-checked against current literature to ensure biological accuracy and consistency with accepted scientific conventions. While schematic figures are designed to simplify complex plant–microbiome–host interactions, they represent conceptual integrations of current evidence rather than exhaustive pathway maps.

The Gastrointestinal Microbiota: A Key Player in Chronic Disease Pathogenesis

The gastrointestinal microbiota is a network of bacteria, viruses, fungi, and archaea that collectively influence numerous physiological processes. It performs a critical function in digestion, immune modulation, and the synthesis of bioactive metabolites [2]. In chronic diseases, the microbiome is often disrupted, resulting in inflammation, altered metabolic function, and impaired immune responses [9]. For instance, in metabolic syndrome, gut dysbiosis can result in heightened gut permeability ("leaky gut"), permitting endotoxins to get into the systemic circulation, triggering chronic low-grade inflammation [10]. Several non-communicable diseases, including metabolic syndrome, cardiovascular diseases (CVDs), and autoimmune disorders, are associated with gut dysbiosis, which is defined by alterations in microbiota composition and function [11]. Dysbiosis is often associated with reduced levels of beneficial metabolites such as short-chain fatty acids and increased levels of potentially harmful metabolites such as trimethylamine N-oxide [12]. These modifications compromise gut barrier integrity, resulting in heightened intestinal permeability and body-wide inflammation [13, 14]. Figure 2 illustrates interactions between phytochemicals, gut microbiota modulation and host pathways relevant to chronic diseases.

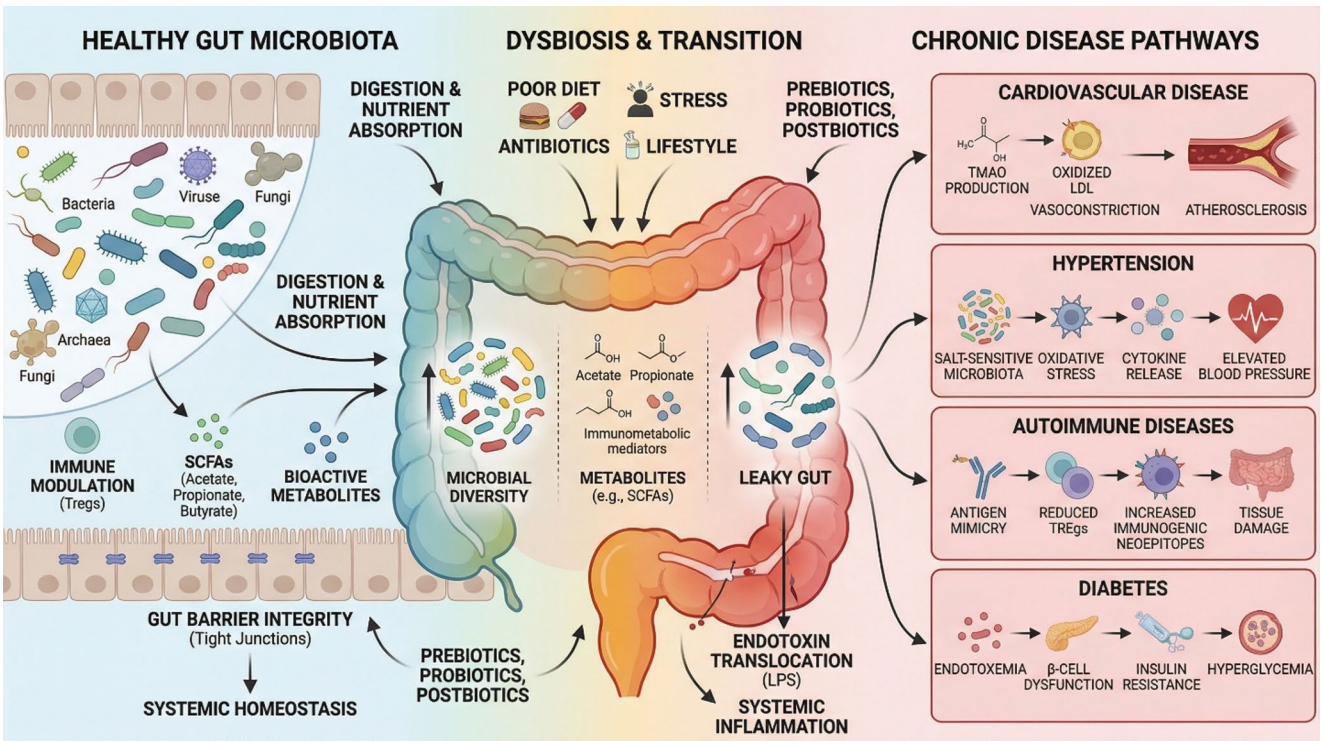


Fig. 2 The gastrointestinal microbiota, including bacteria, viruses, fungi, and archaea, plays a critical role in digestion, immune regulation, and metabolite synthesis; its disruption (dysbiosis) is closely linked with chronic diseases such as metabolic syndrome, cardiovascular disease, autoimmune disorders, and diabetes, through mechanisms involving altered microbial metabolites, increased inflammation, impaired barrier integrity, and immune imbalance

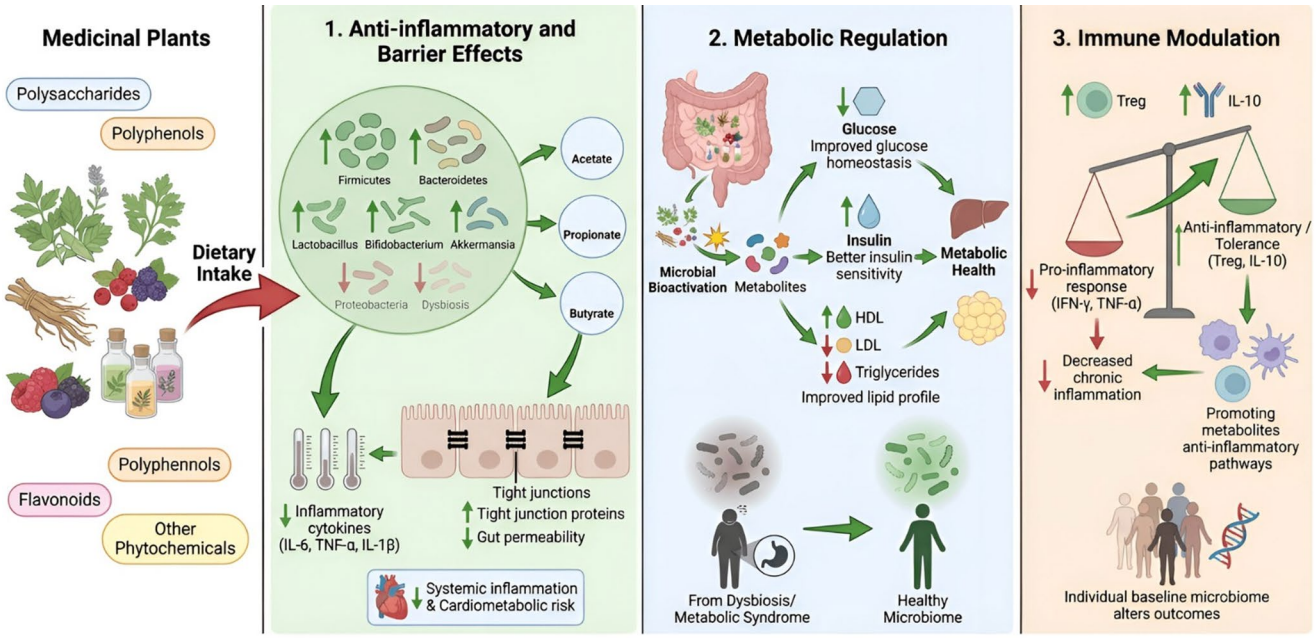


Fig. 3 Integrated mechanistic model illustrating how selected medicinal plants and their bioactive phytochemicals may influence gut microbial taxa, microbial biotransformation, and metabolite production, particularly SCFA-related pathways, with downstream effects on inflammatory, metabolic, immune, and barrier-associated processes relevant to chronic disease. Microbial bioactivation in this figure refers to gut microbial conversion of plant-derived compounds into metabolites with altered or enhanced biological activity

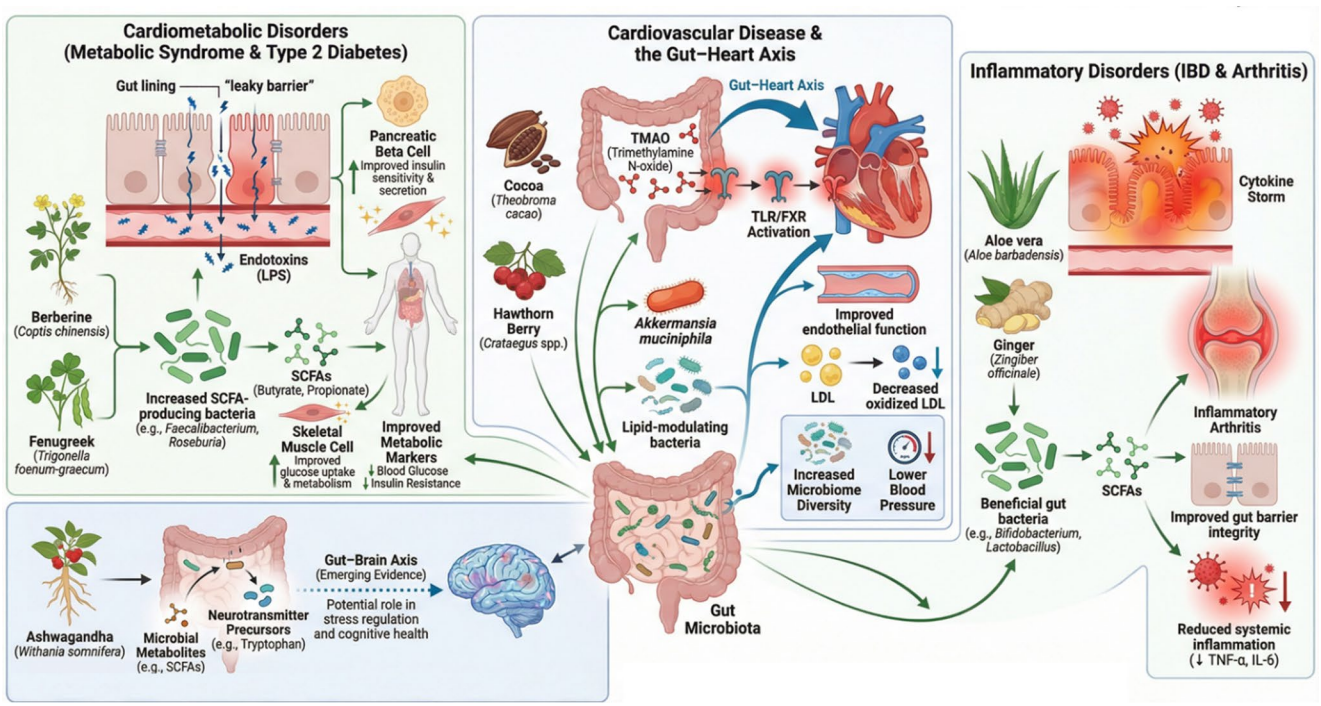


Fig. 4 Disease-cluster synthesis showing how selected medicinal plants are discussed in relation to microbiome-linked mechanisms across cardiometabolic, cardiovascular, inflammatory, and emerging neurodegenerative contexts. Medicinal plants specifically berberine, fenugreek, cocoa, hawthorn berry, aloe vera, ginger, and ashwagandha modulate the gut microbiome and its metabolites (including SCFAs and TMAO) to impact key chronic disease clusters: cardiometabolic disorders, cardiovascular disease (via the gut-heart axis), and inflammatory disorders (IBD and arthritis)

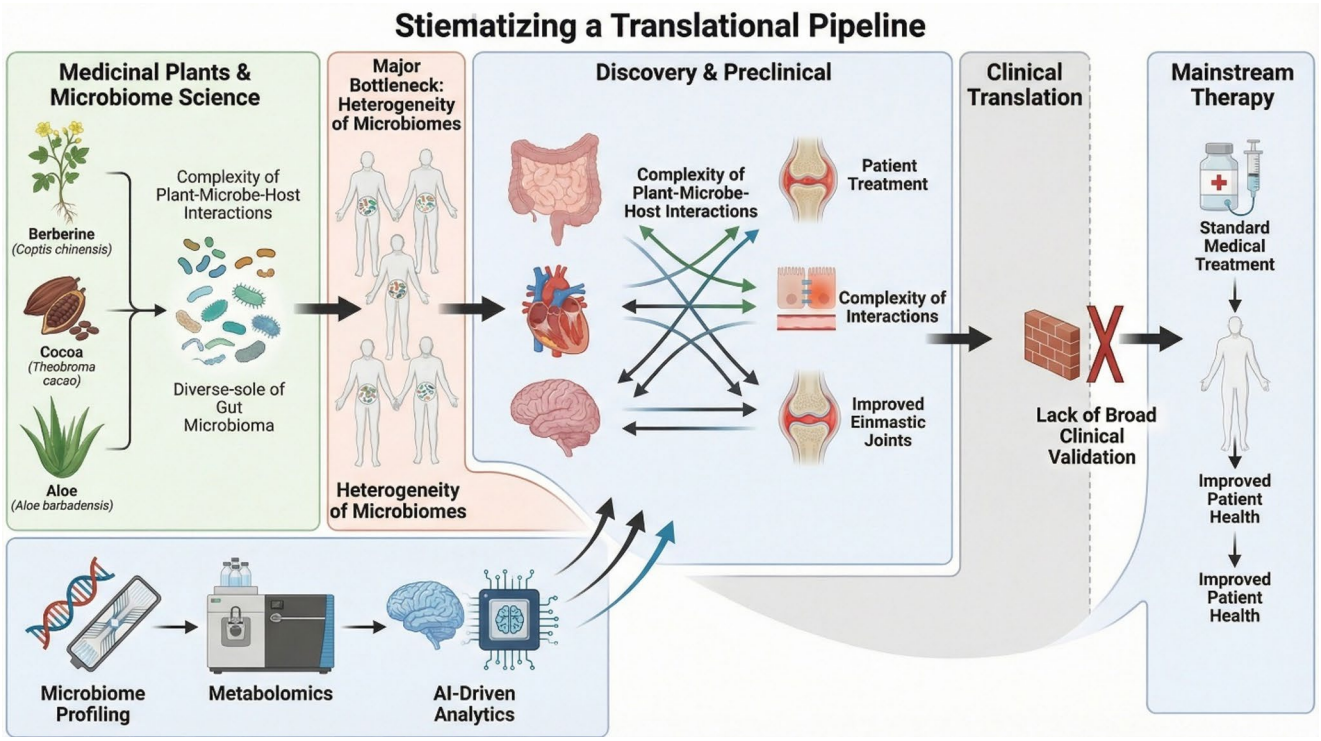


Fig. 5 Translational framework illustrating the major barriers and enabling strategies for moving plant-microbiome research from mechanistic insight toward clinically usable interventions. This highlights key challenges such as microbiome heterogeneity, interaction complexity, and limited clinical validation, while outlining future directions including personalised interventions, microbiome profiling, metabolomics, and AI-driven analytics

Figure 2 repositions dysbiosis itself as a unifying pathological context across chronic disease clusters. It highlights how disrupted microbiota composition and function are linked to inflammatory, metabolic, and immune imbalance across cardiovascular, autoimmune, and diabetic phenotypes. This supports the rationale for why microbiome-targeted plant interventions may be relevant across multiple chronic disease settings. Dysbiosis in cardiovascular diseases activates pathways that contribute to atherosclerosis progression through mechanisms such as toll-like receptor activation and farnesoid X receptor-induced signaling [12]. Experiments involving faecal microbiota transplantation indicate a possible association with dysbiosis of gut microflora [15]. Hypertension is a predominant factor in global disability and mortality [16]. Excessive salt consumption is a risk factor to the onset of hypertension [17]. The gut microbiota is associated with salt sensitivity, as the absorption of sodium primarily takes place in the intestine. Xu et al. [18] detected a rise in bacteria from the *Erwinia* genus and the *Corynebacteriaceae* family in animal models exhibiting hypertension due to high salt intake. An imbalance (dysbiosis) of gut microbiota is specifically connected to hypertension through oxidized of low-density lipoprotein-induced vasoconstriction [19]. The sudden disparity between vasoconstriction and vasodilation is a crucial pathophysiological element in the progress of hypertension. Gut microbiota dysbiosis may contribute to oxidative stress through the release of proinflammatory cytokines. This oxidative stress results in the oxidation of low-density lipoprotein. Elevated oxidized of low-density lipoprotein levels lead to reduced vasodilator production and enhanced vasoconstrictor synthesis, thereby resulting in hypertension [20].

Dysbiosis alters the equilibrium between gut microbiome and the human immune system, potentially resulting in autoimmune illnesses as well as metabolic problems [21]. Dysbiosis makes autoimmune diseases more likely in a number of ways, including by imitating antigens, upsetting the balance of the immune system in the gut, breaking down the intestinal barricades, and lowering the production of substances that fight inflammation [22]. These modifications may result in diminished bacterial diversity, bacterial translocation, inflammation, and a decline in regulatory T cells inside the gut mucosa [23]. Gut microbiota interact with the immune system by controlling host microRNAs and making chemicals that have an effect on cellular receptors. This changes how lymphocytes differentiate and how interleukin is made [24]. Dysbiotic microbiota may cause changes to luminal proteins after they are translated, which could lead to the formation of immunogenic neoepitopes that cause systemic autoimmunity [23]. Understanding

these pathways is important for coming up with new ways to treat autoimmune diseases like type 1 diabetes, multiple sclerosis, rheumatoid arthritis, as well as systemic lupus erythematosus [23].

Research indicates that changes in gut microbial composition correlate with both types 1 and 2 diabetes [25]. Gut dysbiosis may contribute to increased endotoxemia, impaired barrier integrity, and pro-inflammatory responses, all of which may adversely affect β-cell function and promote insulin resistance [25]. The gut microbiota engages with host sensory and signaling networks, influencing the endocrine system, immunological responses, and nervous system function [26]. Diet, antibiotics, and lifestyle factors might affect gut microbial composition, potentially leading to dysbiosis and altering host metabolism to enhance energy extraction during diabetes [27]. Modulating the gut microbiota by prebiotics, probiotics, and postbiotics may provide therapeutic advantages in the management of various disorders [12].

Medicinal Plants as Microbiome Modulators

Medicinal plants are rich in bioactive phytochemicals, including polyphenols, flavonoids, alkaloids, and terpenoids, that are not fully assimilated in the small intestine. These compounds often reach the colon intact, where they interact with gut microbes, modulating their composition and activity.

Phytochemicals as Prebiotics

Certain phytochemicals in medicinal plants have been proposed to exhibit prebiotic-like features and may selectively support the growth of beneficial gut microorganisms. For instance, polyphenols which are present in green tea, berries, and curcumin have been reported in some studies to increase the relative abundance of *Lactobacillus* and *Bifidobacterium*, microorganisms associated with anti-inflammatory and immune-regulatory effects [28]. These compounds also suppress pathogenic bacteria, potentially restoring microbial balance in dysbiotic states. Gut bacteria metabolize numerous phytochemicals like flavonoids, alkaloids, terpenoids, and saponins, which impact the absorption and effectiveness of traditional Chinese medicines [29]. Also, phytochemicals like polyphenols, carotenoids, and thiosulfates are being studied as possible additions to medicines for obesity and inflammatory diseases because they can change the gut microbiota [30]. These discoveries underscore the importance of gut microbiota in influencing the health impacts of dietary phytochemicals.

Microbial Metabolism of Phytochemicals

Gut microbes can metabolise plant-derived phytochemicals into bioactive metabolites that may contribute to some of their reported therapeutic effects. For instance, curcumin from turmeric, poorly absorbed in its native form, undergoes microbial transformation to produce metabolites that have been suggested to possess anti-inflammatory and antioxidant properties [18]. Similarly, ellagitannins from pomegranates are converted by gut microbes into urolithins, compounds with potent anti-inflammatory and anticancer activities [31]. Emerging evidence indicates that these effects are largely mediated through the activation of mitophagy and enhancement of mitochondrial function. Urolithin A has been shown to induce mitophagy, thereby improving cellular energy homeostasis and reducing age-associated mitochondrial dysfunction. Preclinical and clinical studies further demonstrate its role in enhancing muscle function and modulating immune responses, highlighting its therapeutic potential in age-related and metabolic diseases [32–34]. Polyphenols, despite their limited bioavailability, engage in a bidirectional interaction with gut microorganisms, influencing microbial composition while being converted into more bioactive molecules [18]. Overall, microbial biotransformation highlights the functional interplay between medicinal plants and the gut microbiota and supports its consideration in therapeutic strategies.

Common examples of Medicinal Plants

Turmeric, rich in curcumin, has been reported in preclinical dysbiosis models to alter microbial diversity and inflammatory signaling, although robust human microbiome trial evidence remains limited. Despite its limited bioavailability, curcumin influences gut microbiota, potentially explaining its extensive pharmacological effects [18]. Gut bacteria biotransform ginsenosides from ginseng and catechins from green tea, producing compounds with positive benefits [35]. Ginseng saponins are metabolised by gut bacteria into bioactive compounds that have been associated in preclinical and translational studies with improved insulin sensitivity and reduced oxidative stress [36]. Green tea catechins have been reported to modulate gut microbiota and may be associated with lower inflammatory and metabolic risk markers in some settings [37]. Ginseng and green tea provide mechanistically plausible illustrative examples of plant compounds that undergo microbial biotransformation, with reported downstream metabolic and inflammatory effects. However, the strength of evidence varies, and microbiome-linked benefits are often inferred from preclinical studies or human studies with heterogeneous designs. These natural compounds can influence the makeup of intestinal

microbiota, microbial metabolites, and the formation of intestinal tight junctions [38]. The connection between these compounds and gut microbiota is reciprocal: the microbiota influences the absorption and modification of the active compounds, whereas the compounds can also modulate the microbiota [18]. The reciprocal interaction indicates that the gut microbiota may function as a promising therapeutic focus for natural goods, providing novel insights into their mechanisms of action and possible health advantages [18, 38].

Although these botanicals differ in phytochemical composition and do not target identical microbial taxa, the reviewed evidence consistently suggests that many phytoconstituents reach the colon, interact with the gut microbial community, and undergo biotransformation into derivatives with potential anti-inflammatory, metabolic, and immunomodulatory relevance. To bring these evidences together, Table 1 includes a brief summary of exemplary medicinal plants and phytochemicals mentioned in this mini-review and how they fit into the proposed mechanistic model, with changes at taxa levels, changes in microbial metabolism, and the resulting host responses. Where present in the literature used, the table differentiates between human and preclinical evidence. Overall, these botanicals should be interpreted as illustrative case examples of microbiome-mediated potential, not as uniformly established therapeutic interventions. The evidence supporting medicinal plants as microbiome modulators is strongest at the mechanistic level and is derived predominantly from animal studies and in vitro biotransformation research, whereas human evidence remains comparatively limited and heterogeneous.

This table summarises illustrative examples rather than an exhaustive list. Evidence level reflects the highest clearly supported study type cited. Limitations include small sample size, heterogeneity in botanical preparation, variability in microbiome methods, and limited reproducibility across studies.

Synthesis of Evidence Patterns and Gaps

Table 1 illustrates that the evidence base linking medicinal plants to gut microbiota-mediated chronic disease pathways remains uneven and predominantly preclinical. A substantial proportion of the botanicals summarised are supported mainly by animal and mechanistic studies, with comparatively fewer having direct human clinical evidence specifically linking microbiome modulation to clinical outcomes. Even where human studies exist (e.g., berberine, fenugreek, green tea), microbiome endpoints are often secondary, and causal attribution to microbiome-mediated mechanisms remains limited.

Across the reviewed literature, the most consistently supported pathways involve microbial metabolite modulation, particularly short-chain fatty acids (SCFAs), and broad shifts in microbial composition (e.g., enrichment of beneficial taxa). These pathways are frequently linked, at a mechanistic level, to inflammatory, metabolic, and immune-regulatory processes, although direct causal validation in humans is still limited.

Several dominant gaps emerge. First, there is a relative scarcity of well-powered human trials that simultaneously assess botanical interventions, microbiome changes, and clinical outcomes. Second, heterogeneity in botanical preparations (species, extraction methods, dose, and formulation) limits cross-study comparability. Third, variability in microbiome methodologies (sequencing platforms, bioinformatic pipelines, and endpoint selection) constrains reproducibility. Finally, interindividual microbiome variability introduces additional uncertainty in response to plant-based interventions.

Collectively, these patterns indicate that while mechanistic plausibility is strong, the field remains in a transitional phase between preclinical insight and clinically robust, reproducible evidence, underscoring the need for standardized, microbiome-integrated clinical trial designs.

Mechanisms Underpinning Therapeutic Effects

The interaction between medicinal plants and the gut microbiome activates several mechanisms that contribute to chronic disease amelioration. These mechanisms highlight the therapeutic promise of integrating medicinal plants into strategies targeting gut microbiota for chronic disease management (Fig. 3**)**. Figure 3 is central to the mechanistic synthesis because it demonstrates how SCFA-related and other microbiome-derived pathways integrate across the three axes discussed in this review. Specifically, it shows that microbial metabolite production serves as an intermediate layer linking taxonomic shifts to downstream anti-inflammatory, metabolic, and immune effects. By visually connecting plant compounds, microbial taxa, metabolite outputs, and host responses, the figure reinforces the argument that the most plausible microbiome-mediated therapeutic effects depend not only on compositional changes, but also on functional readouts. Across the literature reviewed, the strength of evidence is uneven. Human intervention studies remain comparatively limited, and many mechanistic claims are still driven by animal or in vitro work. Accordingly, statements regarding microbiome modulation, metabolic improvement, or anti-inflammatory benefit should be interpreted on a gradient, from clinical support to

Table 1 Key medicinal plants and their microbiome-mediated mechanisms in chronic disease

Medicinal plant / source	Key phytochemicals	Axis (taxa/metabolites/host)	Microbiome interaction described in manuscript	Functional implication described (as stated)	Evidence level	Critical limitations	Key reference(s)
Turmeric (*Curcuma longa*)	Curcumin	Taxa + (implied) host pathway	↑ diversity; taxa modulation	anti-inflammatory; antioxidant	Animal/mechanistic	Human trial evidence limited; variable formulation and bioavailability; inconsistent microbiome endpoints	[18]
Ginseng	Ginsenosides (saponins)	Metabolites (biotransformation) + host metabolic	Microbial biotransformation	↑ insulin sensitivity; ↓ oxidative stress	Preclinical	Indirect microbiome evidence; variability	[35, 36]
Green tea	Catechins	Taxa + metabolites (biotransformation) + host	taxa shifts; metabolite generation	↓ inflammation markers; metabolic improvement	Preclinical	Limited human microbiome evidence	[35, 37]
Pomegranate	Ellagitannins → urolithins (microbial metabolites)	Metabolites	Converted to urolithins	Anti-inflammatory; anticancer	Mechanistic	Interindividual variability	[31]
Grapes	Resveratrol	Host immune pathway (via microbiome)	Microbiome-mediated immune modulation	Immune modulation via T-reg activation	Mechanistic	Limited human microbiome evidence	[39]
Berries (dietary polyphenol sources)	Polyphenols	Taxa	Polyphenols in green tea, berries, and curcumin reported to enhance Lactobacillus and Bifidobacterium; suppress pathogens; prebiotic-like effect	Anti-inflammatory and immune-regulatory association	Associative	Diet confounding	[40]
Cocoa	Flavonoids	Taxa + cardiovascular host pathway	Modulates lipid-associated microbiota	↑ endothelial function; gut-heart axis	Mechanistic	Limited human evidence	[18] Pan et al., 2023 (Cocoa/hawthorn context)
Fenugreek	Not detailed in this review (medicinal plant example)	Taxa + metabolic host pathway	Reshapes microbiota composition	↑ insulin sensitivity and glucose metabolism	Human evidence present	Small sample sizes; combination interventions can confound attribution	[18]

Table 1 (continued)

Medicinal plant / source	Key phytochemicals	Axis (taxa/metabolites/host)	Microbiome interaction described in manuscript	Functional implication described (as stated)	Evidence level	Critical limitations	Key reference(s)
Berberine (berberine-containing plants)	Berberine	Taxa + metabolic host pathway	Alters microbiota composition	↑ insulin sensitivity and glucose metabolism	Human + preclinical evidence	Small sample sizes; effects vary by diet intake, and dose	[18]
Cinnamon	Not detailed in this review (listed in cited review)	Metabolic host pathway (microbiome link implied	Included among botanicals reviewed for T2DM treatment (microbiome link implied by cited review context)	↑ T2DM-related metabolism	Mechanistic	Indirect evidence	[18]
Bitter melon (*Momordica charantia*)	Not detailed in this review (listed in cited review)	Metabolic host pathway	Included among botanicals reviewed for T2DM treatment	↑ T2DM-related metabolism	Mechanistic	Limited microbiome data	[18]
Ginger	Anti-inflammatory compounds	Host inflammatory pathway + microbiome	Modulates microbial pathways	Anti-inflammatory	Mechanistic	Limited human microbiome data	[41]
Garlic	Thiosulfates; garlic bioactive substances	Taxa/metabolites (candidate phytochemicals)	Microbiota modulation	Immune/metabolic relevance	Mechanistic	Formulation heterogeneity; limited microbiome data	[42, 43]

Abbreviations: T2DM = Type 2 diabetes mellitus; Treg = regulatory T cell; SCFA = short-chain fatty acid. ↑indicates improvement; ↓ indicates decline

Human clinical = randomised controlled trial or controlled human intervention evidence;

Observational = non-randomised human association studies;

Animal/mechanistic = in vivo preclinical evidence;

Mechanistic = in vitro, ex vivo, or metabolite biotransformation evidence

preclinical plausibility, rather than as uniformly established effects. Causal language was avoided unless supported by controlled interventional or mechanistic evidence. Observational and heterogeneous findings are described using associative or suggestive terminology.

Anti-inflammatory Pathways

A primary mechanism is the attenuation of chronic low-grade inflammation via microbiome-derived metabolites and improved gut barrier function [44]. Plant-derived polysaccharides and other fermentable substrates support microbial fermentation, leading to SCFA production, which may influence inflammatory signaling and contribute to maintenance of epithelial barrier integrity [10, 44]. Dysbiosis-associated barrier disruption may increase translocation of luminal microbial products, thereby sustaining systemic inflammation linked to cardiometabolic and inflammatory disease phenotypes [11, 27]. Polyphenols and related phytochemicals may shift microbial composition and metabolite profiles away from pro-inflammatory patterns [11, 40]. In spite of higher mechanistic resolution in experimental systems, human studies primarily report associative relationships between SCFA-related signatures, barrier markers, and clinical outcomes [11, 44]. While these pathways primarily relate to inflammatory regulation and barrier function, overlapping microbiome-derived signals also influence immune-cell activity, as discussed below.

Metabolic Regulation

Medicinal plant-derived phytochemicals may contribute to improved glucose homeostasis and lipid profiles through microbiome-mediated pathways, thereby reducing risk phenotypes associated to metabolic syndrome and type 2 diabetes [7, 45]. Many phytochemicals have limited absorption rate in the small intestines, and as such, they are built up in the colon, biotransformed by gut microbiota into metabolites whose bioactivity and bioavailability is altered. This term, referred to as microbial bioactivation may alter systemic metabolic effects relative to the parent compound alone [29, 38]. Mechanistically, the recorded changes can intersect with insulin resistance, which is mediated by inflammation. Dysbiosis is associated with impaired metabolism, due to the effects of inflammatory signaling pathways and changes in host-microbe metabolic interactions, which makes microbiome-targeted phytotherapeutic interventions a promising approach to improving insulin sensitivity and metabolic resilience [26, 27]. In this framework, the therapeutic relevance lies not only in compositional changes but also in functional changes, that is, whether the intervention increases beneficial metabolite production and may contribute to dysbiosis-associated metabolic outputs relevant to cardiometabolic risk [7, 11]. Thus, current evidence for microbiome-mediated metabolic benefits is biologically plausible and supported by animal and mechanistic studies, with emerging but still limited confirmation from human intervention studies.

Immune Modulation

While inflammatory signaling and immune regulation are closely linked, they are treated here as related but distinct layers: the former focuses on chronic low-grade inflammatory pathways and barrier dysfunction, whereas the latter addresses microbial effects on immune-cell activity and host immune balance. Other than suppressing inflammation, medicinal plants may influence immune balance by shaping microbial cues and metabolites that dictate the mucosal and systemic immunological balance. Microbiome-immune crosstalk is one such central axis of homeostasis of immune regulation and dysbiosis with associated impaired immune regulation has been implicated in the development of inflammatory and autoimmune phenotype [21, 24]. Plant and microbiome-derived SCFAs are often described as immunometabolic signalling molecules that may influence immune cell activity and epithelial-immune cell communication [21, 44]. For instance, resveratrol from grapes activates regulatory T-cells through microbial interactions [39]. Notably, immune effects are likely to vary across individuals because baseline microbiome configuration shapes metabolite production and host responsiveness. Accordingly, mechanistic interpretation should account for interindividual variability and the frequent gap between preclinical mechanistic clarity and heterogeneous clinical outcomes in human studies. Immune responses are likely to vary across individuals because baseline microbiome composition regulates the production of metabolites and host receptiveness. As a result, mechanistic interpretations should integrate interindividual variability and recognise the frequent gap between preclinical mechanistic certainty and heterogeneity of clinical outcomes in human research [46, 47]. Together, the immune-modulatory role of medicinal plants through the microbiome is supported mainly by preclinical and mechanistic evidence, whereas human evidence remains less consistent and requires further validation in controlled trials.

Interpretation Boundaries (What can be Claimed Mechanistically vs. associated)

Since botanical preparations, doses, and microbiome endpoints are heterogeneous, mechanistic claims should be scaled to evidence level. Human studies frequently support associations between plant interventions, microbiome shifts, and metabolic/inflammatory outcomes, whereas causal resolution is stronger in controlled experimental designs that quantify functional outputs (metabolites, barrier markers) alongside microbial changes [11, 47]. Therefore, the most defensible mechanistic statements are those that (i) explicitly include microbial functional readouts (like SCFA-related profiles), (ii) align with dysbiosis-linked disease pathways already described in this review, and (iii) acknowledge baseline microbiome variability as a determinant of response. In this context, the mechanistic claims that can be most readily defended are those claims that (i) consider the microbial functional readouts (like SCFA-related profiles), (ii) are consistent with the disease pathways that have previously been outlined in this review, and (iii) take into account the baseline variability of microbiomes as a predictor of therapeutic outcome [46, 47].

Medicinal Plants Potential for Chronic Disease Management

The therapeutic relevance of medicinal plants in chronic disease management is most apparent in disease clusters where microbiome–metabolite–host interactions are most consistently described. The most comprehensively developed associations in this review all focus on (i) cardiometabolic disorders, (ii) cardiovascular disease and the gut-heart axis, and (iii) inflammatory disorders wherein dysbiosis-associated changes in microbial metabolites (e.g., reduced

beneficial SCFAs and increased harmful metabolites such as trimethylamine N-oxide) and impaired gut barrier function contribute to systemic inflammation and downstream pathology (summarised in Fig. 4). Figure 4 provides a disease-oriented synthesis by mapping specific botanicals onto the chronic disease clusters in which microbiome-related mechanisms are most frequently discussed. It shows that the strongest patterns in the current literature are concentrated in cardiometabolic, cardiovascular, and inflammatory conditions, while other areas, such as neurodegeneration, remain more exploratory.

Cardiometabolic Disorders (Metabolic Syndrome and Type 2 Diabetes)

Gut dysbiosis is implicated in metabolic syndrome through increased intestinal permeability ("leaky gut"), which facilitates systemic exposure to endotoxins and promotes chronic low-grade inflammation. Medicinal plants that reshape microbiota composition and support the abundance of beneficial metabolite-producing bacteria are of particular interest. Medicinal plants such as berberine and fenugreek have been associated with improved glycemic outcomes in human and preclinical studies, partly by modifying gut microbiota composition and promoting SCFA–producing bacteria, which may attenuate inflammation and support metabolic health [18, 48]. However, interpretation should remain cautious because available studies differ in sample size, formulation, co-interventions, and microbiome methodology. Overall, evidence for microbiome-linked effects in cardiometabolic disorders includes both human and preclinical studies, but mechanistic resolution remains stronger in experimental systems than in clinical trials.

Cardiovascular Disease and the Gut-heart Axis (Including Hypertension)

Cardiovascular disorders are strongly connected to dysbiosis-associated metabolic and inflammatory signaling, including changes in microbial metabolites and receptor-mediated pathways that contribute to atherosclerosis progression. In this perspective, cardiovascular dysbiosis is described as activating atherosclerosis-related mechanisms such as toll-like receptor activation and farnesoid X receptor–induced signaling, and it is also linked to an imbalance between vasoconstriction and vasodilation in hypertension through oxidative stress and oxidized low-density lipoprotein-associated pathways. Flavonoids in medicinal plants like cocoa and hawthorn berry have been reported to support endothelial function and may also be associated with changes in gut bacteria linked to lipid metabolism [18]. This dual action suggests potential relevance to the gut-heart axis in cardiovascular disease. In human cohorts, gut microbiome features (diversity and specific taxa patterns) have been reported to be associated with blood pressure phenotypes, though findings vary across populations and analytic pipelines [49, 50]. In animal and ex vivo studies, microbiome perturbation and microbially derived metabolites have been shown to influence host vascular tone, oxidative stress signaling, and immune activation, supporting a plausible mechanistic link between dysbiosis and hypertensive phenotypes [51]. For cardiovascular outcomes, the microbiome evidence is biologically plausible but still variable in reproducibility across cohorts, partly due to differences in population characteristics, sequencing pipelines, and definitions of dysbiosis. Human evidence mainly supports associations between microbiome features and cardiovascular phenotypes, while causal and mechanistic support is derived more strongly from animal and ex vivo studies.

Inflammatory Disorders (IBD and Arthritis as Exemplars)

Inflammatory diseases provide another clinically relevant cluster because dysbiosis is repeatedly associated with impaired immune regulation and amplified inflammatory signaling. In this review, aloe vera and ginger are presented as examples of plants rich in anti-inflammatory compounds that influence gut microbial pathways, with reported relevance to inflammatory conditions such as inflammatory bowel disease and arthritis [41]. As noted in the mechanism section, microbial metabolites (notably SCFAs) are linked to cytokine modulation and improved gut barrier integrity, processes directly relevant to chronic inflammatory phenotypes [52]. However, the relevance of medicinal plants in inflammatory disorders is currently supported primarily by mechanistic and preclinical evidence, with comparatively limited direct human microbiome-linked intervention data.

Emerging Area: Gut-brain Axis and Neurodegenerative Conditions

The gut-brain axis is an emerging dimension mediated by microbial metabolites such as SCFAs and neurotransmitter precursors. However, the evidence summarised here remains less developed than the cardiometabolic, cardiovascular, and inflammatory clusters. Accordingly, neurodegenerative applications are best framed as a forward-looking area, exemplified by medicinal plants such as ashwagandha, which is described as potentially influencing microbiota in relation to stress and cognitive decline [53]. There is insufficient human trial data to support firm translational conclusions.

Challenges and Knowledge Gaps

Despite the promise, integrating medicinal plants and microbiome science into mainstream therapy faces challenges:

i. ***Heterogeneity of Microbiomes***: Individual variability in gut microbiome composition can lead to differing therapeutic outcomes. Standardization of plant-derived compounds, interindividual variability in microbiome composition, and limited understanding of plant-microbiome-host interactions are significant hurdles [46]. This necessitates personalized approaches to plant-based interventions.
ii. ***Complexity of Interactions***: The bidirectional interaction between phytochemicals and gut microbes involves multiple pathways, making it challenging to isolate specific effects. Advances in multi-omics technologies and computational modeling could unravel these complexities, enabling personalized interventions [54].
iii. ***Clinical Validation***: Although preclinical studies provide compelling mechanistic insight, large and well-controlled clinical trials linking medicinal plant use, microbiome modulation, and chronic disease outcomes remain limited [47]. Moreover, clinical trials are needed to validate the effectiveness of plant-microbiome treatments in chronic diseases.
iv. ***Reproducibility and methodological consistency***: Reproducibility remains limited across plant-microbiome studies because of variation in sample size, baseline diet, medication exposure, geography, botanical identity, extraction methods, sequencing platforms, and bioinformatic pipelines. These factors complicate cross-study comparison and weaken confidence in generalised conclusions.

Despite the evident promise expressed in the mechanistic and disease-focused sections, the translation of these findings into practical therapies is still hampered by the frequent challenges that have been noted in this review, specifically, interindividual heterogeneity of microbiomes, the complexity of plant-microbe-host interactions, and the lack of the broad clinical trials that could simultaneously investigate botanicals, microbiome modulation, and clinical outcomes. To illuminate where the bottlenecks occur and to outline the possible remedial measures Fig. 5 sketches a translational pipeline between the discovery and implementation, and charts the enabling actions suggested in the Future Directions section such as microbiome profiling, metabolomics, and AI-driven analytics. Figure 5 extends the review beyond mechanism by synthesising the translational bottlenecks that currently prevent routine clinical application. It shows that microbiome heterogeneity, interaction complexity, and limited clinical validation are not isolated problems, but interconnected barriers spanning discovery, standardisation, and implementation. In this way, the figure provides a bridge between the knowledge-gap section and the future-directions section by illustrating where enabling tools such as microbiome profiling, metabolomics, and AI-driven analytics may have the greatest impact.

Safety, Standardisation, and Microbiota-Relevant Herb-Drug Interactions

Even though medicinal plants and their phytochemicals have the capacity to regulate gut microbiota and microbial metabolites, their clinical translation must be evaluated in terms of safety, product standardization, and microbiota-relevant herb-drug interactions. Variability in botanical identity, plant part used, cultivation source, extraction method, processing, and formulation can substantially alter phytochemical composition and thereby affect reproducibility of microbiome-related outcomes [55]. This is consistent with the heterogeneity and gaps in clinical validation that were echoed in this review. For this reason, studies should report minimum characterization standards, including correct botanical authentication, preparation details, dose form, administered dose, and quality testing for contaminants or batch variability, so that microbiome findings can be interpreted with greater confidence [18].

Standardisation is critical for interpreting microbiome outcomes and enabling cross-study comparisons. Consistent characterisation consists of authentication and traceability, chemical fingerprinting with the quantification of markers, batch-to-batch consistency targets, and in some cases screening of impurities or contaminants [56]. Such requirements form the basis of reproducibility and provide a more conclusive basis to make the associations of a given botanical preparation with changes in the microbiome, and clinical outcomes.

One of the key translational barriers is herb-drug interaction, especially for chronic disease patients who are often involved in polypharmacy. Some botanicals have the ability to alter drug-metabolic enzymes and gastrointestinal transporters, and thus, affect the systemic exposure to co-administered drugs [57]. Thus, interaction-conscious safety measures, which include organised medication histories, elimination/stratification criteria of high-risk interactions, standardised adverse-event reporting procedures, and, in case of narrow-therapeutic-index medications, the use of pharmacokinetic/pharmacodynamic monitoring where possible should be included in clinical studies. A notable example is the St. John's wort which poses a significant interaction risk because of its induction of P450 cytochrome

enzymes and intestinal P-glycoprotein transporters leading to lower blood levels of many therapeutics used, such as immunosuppressants, antiretrovirals, oral birth control, anticoagulants, and digoxin [58]. Although St. John's wort remains an important example of classical enzyme- and transporter-mediated herb-drug interaction, microbiota-dependent drug modification represents an additional and increasingly important translational layer that is directly relevant to plant-based interventions in chronic disease. In order to add to clinical plausibility, future studies on plant-microbiome interactions should include standardised botanical characterisation, stringent safety monitoring as well as explicit evaluation of potential risks of interaction. It is expected that the combination of microbiome profiling with metabolomics and other multi-omics technologies (as suggested in Future Directions), will lead to increased precision in mechanistic resolution, enable the determination of responder phenotypes and enhance reproducibility between different cohorts.

Beyond classical herb-drug interactions mediated by hepatic enzymes and transporters, accumulating evidence shows that the gut microbiota itself can directly influence drug efficacy, bioavailability, and toxicity. This concept, often described within pharmacomicrobiomics, highlights that interindividual differences in microbial composition and function may contribute to variable therapeutic response [59]. For example, the cardiac drug digoxin can be inactivated by the gut bacterium *Eggerthella lenta*, reducing active drug exposure in some individuals [60]. Similarly, gut bacteria can metabolize levodopa through an interspecies pathway, lowering drug availability before absorption [61]. In cancer therapy, intestinal bacterial β-glucuronidase activity contributes to irinotecan gastrointestinal toxicity by regenerating toxic metabolites in the gut lumen, and selective inhibition of these microbial enzymes has improved tolerability in experimental models [62]. These examples demonstrate that the microbiota is not merely a passive background factor, but an active determinant of drug response.

This microbiota-dependent perspective is directly relevant to medicinal plants because many chronic disease patients use botanicals alongside conventional medicines. Plant-derived compounds may influence microbial composition and metabolic activity, while the same microbial ecosystem may also modify co-administered drugs. Thus, future studies should evaluate herb-drug interactions not only through conventional pharmacokinetic pathways, but also through microbiota-dependent co-metabolism, particularly where both botanicals and prescribed drugs may converge on shared microbial enzymes or metabolite networks. Clinical studies would therefore benefit from structured medication histories, exclusion or stratification for high-risk interactions, adverse-event monitoring, and, where feasible, incorporation of microbiome profiling and metabolomic readouts to identify responder and risk phenotypes [59].

Accordingly, the most clinically informative next-generation trials in this area should combine standardised botanical characterisation, rigorous safety monitoring, and microbiome-aware assessment of therapeutic response. Integrating microbiome profiling with metabolomics and other multi-omics tools may improve mechanistic resolution, identify subgroups most likely to benefit or experience adverse effects, and enhance reproducibility across cohorts.

Future Directions

The integration of medicinal plants and gut microbiome research offers several important opportunities for future investigation and translation. Advances in gut microbiome profiling and bioinformatics may enable more tailored plant-based interventions aligned with individual microbiome signatures, thereby supporting the development of personalised strategies. In addition, combining medicinal plants with probiotics or prebiotics may enhance therapeutic efficacy through complementary or synergistic mechanisms. Emerging technologies, including AI-driven microbiome analysis, metabolomics, and broader multi-omics integration, may further clarify plant-microbiome interactions and accelerate mechanistic discovery. At the same time, meaningful progress in this field will require interdisciplinary collaboration among ethnobotanists, microbiologists, pharmacologists, and clinical researchers to ensure that mechanistic insights are effectively translated into clinically relevant applications.

To move this field beyond descriptive associations and toward clinically reliable plant-microbiome interventions, it is crucial to link the key barriers identified in this review with practical solutions that are feasible for near-term research and translation. Table 2 synthesises the major challenges highlighted (microbiome heterogeneity, mechanistic complexity, and limited clinical validation) and aligns them with enabling strategies emphasised in the Future Directions section, including personalised microbiome profiling, integrated multi-omics/metabolomics, AI-driven analysis, and interdisciplinary collaboration.

Toward Clinically Actionable Plant–microbiome Interventions

To move beyond descriptive associations and toward clinically actionable plant-microbiome interventions, future research should adopt integrated and standardised study designs that explicitly connect botanical exposure,

Table 2 Challenges and solutions for translating plant-microbiome research

Challenge (as stated)	Why it matters (impact on interpretation/translation)	Practical solution (aligned to manuscript)
Interindividual microbiome heterogeneity	Different baseline microbiomes can produce variable responses to the same plant-based intervention, limiting reproducibility and generalizability.	Adopt microbiome profiling and stratified designs to support tailored plant-based therapies and improve responder identification (personalized medicine approach).
Complexity of bidirectional plant–microbe–host interactions	Multiple interacting pathways make causality difficult to isolate and can lead to inconsistent mechanistic interpretations across studies.	Use integrated multi-omics and computational approaches to disentangle pathways and link phytochemicals, microbial shifts, and functional outputs.
Limited large-scale clinical validation	Small or heterogeneous clinical evidence reduces confidence in clinical effectiveness and slows translation into practice.	Increase well-controlled clinical trials that explicitly connect botanical interventions, microbiome modulation, and clinical outcomes.
Need for enabling technology and mechanistic biomarkers	Without validated biomarkers, it is difficult to track response, compare studies, or personalize interventions reliably.	Apply metabolomics and broader multi-omics to identify mechanistic biomarkers; use AI-driven analysis to accelerate discovery and signal detection.
Implementation requires cross-field expertise	Fragmented evidence across ethnobotany, microbiology, and clinical research can delay translation and standardization.	Promote interdisciplinary partnerships to integrate discovery, mechanistic work, and clinical testing.

microbiome dynamics, and clinical outcomes. Randomised controlled trials should incorporate baseline microbiome stratification, grouping participants according to microbial composition or functional profiles, such as SCFA-producing capacity or enterotype-like clusters. This may help identify responder and non-responder phenotypes and address the well-recognised issue of interindividual variability. Crossover designs may be particularly useful in early-phase studies because they help control for interpersonal microbiome differences. In addition, multi-arm trial designs, for example comparing botanical intervention alone, botanical plus prebiotic or probiotic co-intervention, and placebo, may help disentangle direct effects from microbiome-mediated effects.

Botanical standardisation will also be essential for reproducibility. Future studies should adopt standardised characterisation protocols that include taxonomic authentication, plant part specification, extraction method, and quantitative phytochemical profiling, such as marker compound concentration. Dose, formulation, whether whole extract or purified compound, and duration should be clearly defined and justified. Reporting batch-to-batch consistency and contaminant screening would further improve interpretability and comparability across studies.

Table 3 Translational Study Design for Plant–Microbiome Interventions

Component	Recommendation
Study design	Randomised, placebo-controlled, microbiome-stratified trial
Population	Stratified by baseline microbiome (e.g., SCFA producers vs. low producers)
Intervention	Standardised botanical extract with defined phytochemical content
Comparator	Placebo ± microbiome co-intervention (e.g., probiotic/prebiotic)
Outcomes	Clinical endpoints + microbiome composition + metabolomic biomarkers
Duration	≥ 8–12 weeks to allow microbiome adaptation
Analysis	Responder vs. non-responder subgroup analysis; multi-omics integration

A robust translational framework should also include multilayered microbiome and biomarker strategies. Future trials should integrate microbial composition measures, such as 16 S rRNA sequencing or metagenomics, with functional outputs including SCFA profiles, bile acid metabolism, and broader metabolomic signatures, alongside host-response markers such as inflammatory cytokines, metabolic indices, and barrier integrity markers. Importantly, microbiome outcomes should be prespecified rather than treated as exploratory, and they should be aligned with clinically meaningful endpoints.

Finally, harmonisation of microbiome pipelines, including sequencing platforms, bioinformatic workflows, and reporting standards, will be critical for reproducibility. Integration of multi-omics approaches with computational modeling, including AI-driven analytics, may further support identification of mechanistic pathways and predictive biomarkers of response.

Collectively, these strategies provide a pathway for translating mechanistic insights into clinically testable, reproducible, and personalised plant–microbiome interventions, addressing key barriers identified in this review. Without such structured approaches, the field may remain at the level of mechanistic plausibility rather than progressing toward clinically actionable and reproducible therapeutic strategies. To operationalise the translational recommendations outlined above, Table 3 provides a structured example of a microbiome-integrated clinical trial design. This framework aligns botanical standardisation, microbiome stratification,

and multi-layered outcome assessment within a single study architecture. It illustrates how future trials can move beyond descriptive associations toward reproducible, mechanism-informed clinical evaluation of plant–microbiome interactions.

Table 3 summarises key elements of a translationally oriented clinical trial integrating medicinal plants and gut microbiota analysis. It highlights the importance of microbiome stratification, botanical standardisation, and multi-layered biomarker assessment to improve reproducibility and clinical relevance. This table presents an illustrative framework rather than a prescriptive protocol. Specific design elements should be adapted based on disease context, botanical properties, and study population.

Conclusion

Medicinal plants, through their interaction with the gut microbiome, represent a promising area of investigation in chronic disease management. By modulating microbial communities and influencing beneficial metabolic pathways, they may support microbiome-informed approaches to chronic disease prevention and adjunct management. However, the current evidence base remains uneven: mechanistic support is substantial in animal and in vitro systems, whereas human evidence, although growing, remains heterogeneous and often associative rather than definitive. Future progress will depend on well-controlled human trials, standardised botanical characterisation, and integrated microbiome-functional readouts that can more clearly link microbial changes to clinical benefit. In addition, interdisciplinary collaboration across microbiology, pharmacology, clinical science, and systems biology will be important for advancing this field. As understanding of the gut microbiome continues to expand, medicinal plants may emerge as useful adjuncts within sustainable and personalised strategies for chronic disease management, rather than as definitive standalone therapeutic solutions.

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Declarations

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