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REVIEW

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Modulatory role of plant-derived metabolites on host-microbiota interactions: personalized therapeutics outlook

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Key words: Microbiome therapeutics, Human gut microbiota, Host-microbiota interactions, Personalized therapeutics, Plant metabolites, Human health and diseases

Abstract: A diverse array of microbes in and on the human body constitute the microbiota. These micro-residents continuously interact with the human host through the language of metabolites to dictate the host's physiology in health and illnesses. Any biotic and abiotic component ensuring a balanced host-microbiota interaction are potential microbiome therapeutic agents to overcome human diseases. Plant metabolites are continually being used to treat various illnesses. These metabolites target the host's metabolic machinery and host-gut microbiota interactions to overcome human diseases. Despite the paramount therapeutic significance of the factors affecting host-microbiota interactions, a comprehensive overview of the modulatory role of plant-derived metabolites in host-microbiota interactions is lacking. The current review puts an effort into comprehending the role of medicinal plants in gut microbiota modulation to mitigate various human illnesses. It would develop a holistic understanding of host-microbiota interactions and the role of effectors in health and diseases.

Introduction

Continuous exposure to microorganisms allowed their settlement in and on the human body, collectively known as human microbiota [1]. The diversity and abundance of these microorganisms vary with human anatomical locations [2]. Among all anatomical locations, the human gut microbiota is highly dense, contributes ~10% of body weight, and extends the protein-coding efficiency of the host by 90% [3]. Despite the abundance, the gut microbiota is represented primarily by Bacteroidetes and Firmicutes, followed by many minor microbial species [4]. Many variables, like host genetics, epigenetics, environmental, dietary preferences, lifestyle, etc., define the host's gut microbiota composition [5]. Our understanding of this significant ecosystem's complexity has been entirely transformed by the capacity to characterize the genetic repertoire of bacterial populations without cultivating each bacterium [6,7]. These gut residents catabolize various dietary constituents and release metabolites such as Short-chain fatty acids (SCFAs), polyamines, tryptophan metabolites, etc., in the surrounding environment, which finally reaches the host biological system through absorption [8]. These metabolites alter the host cellular expression profile and influence host physiology. This metabolic crosstalk between microbiota and host regulates various physiological processes to ensure human health [9]. A pathogen invasion or gut microbiota dysbiosis evokes healthy cross-talk. It induces a host inflammatory response [10], leading to the onset of various illnesses and pathologies, including obesity, inflammatory bowel disease (IBD), autoimmune diseases, allergies, respiratory diseases, and neurological conditions [11,12]. Host-microbiota interactions were a prime target for overcoming gut dysbiosis-derived human illnesses [13]. Understanding the importance of host-microbiota crosstalk, any molecule with potential therapeutic properties towards restoring the microbiota equilibrium is critical.

Consumption of plants and plant metabolites generates microbial metabolites such as SCFAs and bio-transformed plant metabolites [14]. These metabolites include carotenoids, alkaloids, polyphenols, organosulfur, and nitrogen-containing compounds [15]. The subsequent absorption of these metabolites into the bloodstream mediates several host-microbe actions and influences host health [16]. Plant and plant-derived compounds have been utilized for a long time for their therapeutic applications to overcome various illnesses [17]. This might be attributed to

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plant-derived metabolites' antioxidant, anticancer, antibacterial, and anti-inflammatory properties [17]. Recent studies revealed an association between gut microbiota dysbiosis and the onset of human illness [18,19]. So, if plant and plant-derived compounds effectively treat gut microbiota dysbiosis-induced illnesses, these compounds also regulate microbiota interactions to restore health [17]. Only a few isolated studies indicated their role in host-microbiota interactions and gut epithelial integrity. However, a comprehensive overview of decoding how these microbiota influence host-microbe interactions is still awaited. This review will develop a holistic understanding of host-microbiota interactions in health and diseases and comprehend the mechanistic role of plant metabolites in these molecular bioprocesses.

Host-Microbe Interactions

The host-microbe interacts via the gut microbiota-derived metabolites and host immunological response [9]. The human-microbe interaction co-evolves for the benefit of both members, where the human host provides a nutrient-rich safe harbor [20]. At the same time, microbes offer a litany of microbial metabolites, which benefit host physiology and resistance to competitive pathogens [21]. The predominant metabolites are SCFAs, tryptophan metabolites, bile acids, and choline metabolite [22]. These metabolites affect the host physiology by modulating various cellular processes (Fig. 1). SCFAs are derived from bacterial fermentation and play a pivotal role in bodily functioning and the modulation of the immune system [23]. SCFAs, such as acetate, propionate, and butyrate, are synthesized in the gastrointestinal tract and are absorbed by the intestinal epithelial cells (IECs), lining the intestine, to serve as an energy source [24]. They also connect the gut microbiota and the immune system, influencing the development, survival, and function of both IECs and leukocytes [25]. SCFAs exert their effects by activating specific receptors, namely Free fatty acid receptor 2 (FFAR2), FFAR3, G-protein coupled receptor 109a (GPR109a), and Olfactory receptor 78 (Olfr78), and by modulating the activity of enzymes and transcription factors [26]. SCFAs also regulate the functioning of regulatory T cells (Treg) and foster immune tolerance, indicating their potential therapeutic implications for inflammatory disorders [27]. The gut microbiota metabolizes the tryptophan in the intestinal lumen into kynurenine, tryptamine, and indole [28]. Indole and indole-3-propionate (IPA), affect mucosal homeostasis through the pregnane X receptor (PXR) and reduce intestinal permeability. Indole also stimulates enteroendocrine L-cells to release glucagon-like peptide 1 (GLP-1), suppressing appetite, insulin secretion, and gastric emptying [29]. Several tryptophan catabolites modify innate and adaptive immune responses in intestinal immune cells by activating aryl hydrocarbon receptors (AHR), thus maintaining mucosal reactivity [30]. Tryptamine enhances gastrointestinal motility by inducing the enterochromaffin cells to secrete the 5-hydroxy tryptamine (5-HT), acting on enteric nervous system neurons [31]. Gut microbes alter lipid metabolism by producing secondary bile metabolites. Iso-allo Lithocholic acid (LCA), a microbiota-derived metabolite, promotes the Treg population, while cells and 3-oxo Lithocholic acid (3-oxoLCA) inhibit suppression of the T helper-17 (TH17) population [32]. (Fig. 1).

Host immunological response is another facet of the host-microbiota bidirectional cross-talk. The intestinal immune system constantly works to maintain equilibrium between bacterial tolerance and being vigilant against pathogens [33,34]. The immune system and the microbiota communication is mediated by a large set of proteins called pattern recognition receptors (PRRs). These PRRs are synthesized by various hematopoietic cells and IECs [35]. PRRs that identify microbe-associated molecular patterns (MAMPs) include nuclear oligomerization domain-like receptors (NLRs) and toll-like receptors (TLRs) [35,36]. Previous studies have reported that the loss of particular PRRs can result in changes to the composition of microorganisms and intestinal barrier issues, which allows microorganisms to infiltrate systemic organs [37]. TLR deficiency was found to cause longer-term familial changes in microbial composition, although the ileal microbiota composition in TLR2-, TLR4-, TLR5-, and TLR9-deficient mice was demonstrated to stay constant in the short term [38]. It can be deduced that host-microbe interactions are interdependent as NOD-like receptor family pyrin domain containing 6 (NLRP6) deficiency in mice is associated with decreased tissue repair efficiency by interleukin-18 (IL-18)-dependent pathway along with an altered colonic microbiota enriched in the *Prevotellaceae* and *Saccharibacteria* TM7 [39]. The adaptive branch of the immune system functions via Immunoglobulin A (IgA) antibodies, which act as a bridge between the innate and immune systems in the intestine [40]. Gene knock-out studies point towards the integrative role of IgA in recognizing the intestinal microbiota, particularly commensals [41]. Bacteria penetrating through the mucus layer leads to class switching of B cells and subsequently produces IgA. These IgA are secreted into the intestinal lumen, which recognizes the microbiota [42]. The host repertoires of IgA are specific to particular bacterial epitopes of commensals and coat most of the intestinal microbiota without causing strong and potentially harmful reactions [43]. The repertoire of secreted IgA is continuously changing to adapt and respond to the fluctuating intestinal microbial environment. This repertoire may be dynamically shaped to mirror the microbiota composition [44]. Other immune cells, i.e., T regulatory type 1 (Tr1) cells, T helper (TH17) cells, and Treg cells, aid the IgA-dependent microbiota interactions [45]. Although the immune system protects the gastric microbiota, the pathogens utilize this for their growth benefit [46]. Immune defense against pathogens leads to intestinal barrier disruption, inflammation, and secretion of inflammatory molecules like tetrathionate and nitrates [47]. These molecules aid the growth of pathogens like *Salmonella typhimurium* and *Escherichia coli* [48].

Host-Microbe Interactions in Disease

Host-microbe interactions play a significant role in maintaining gut homeostasis and human health [49]. These

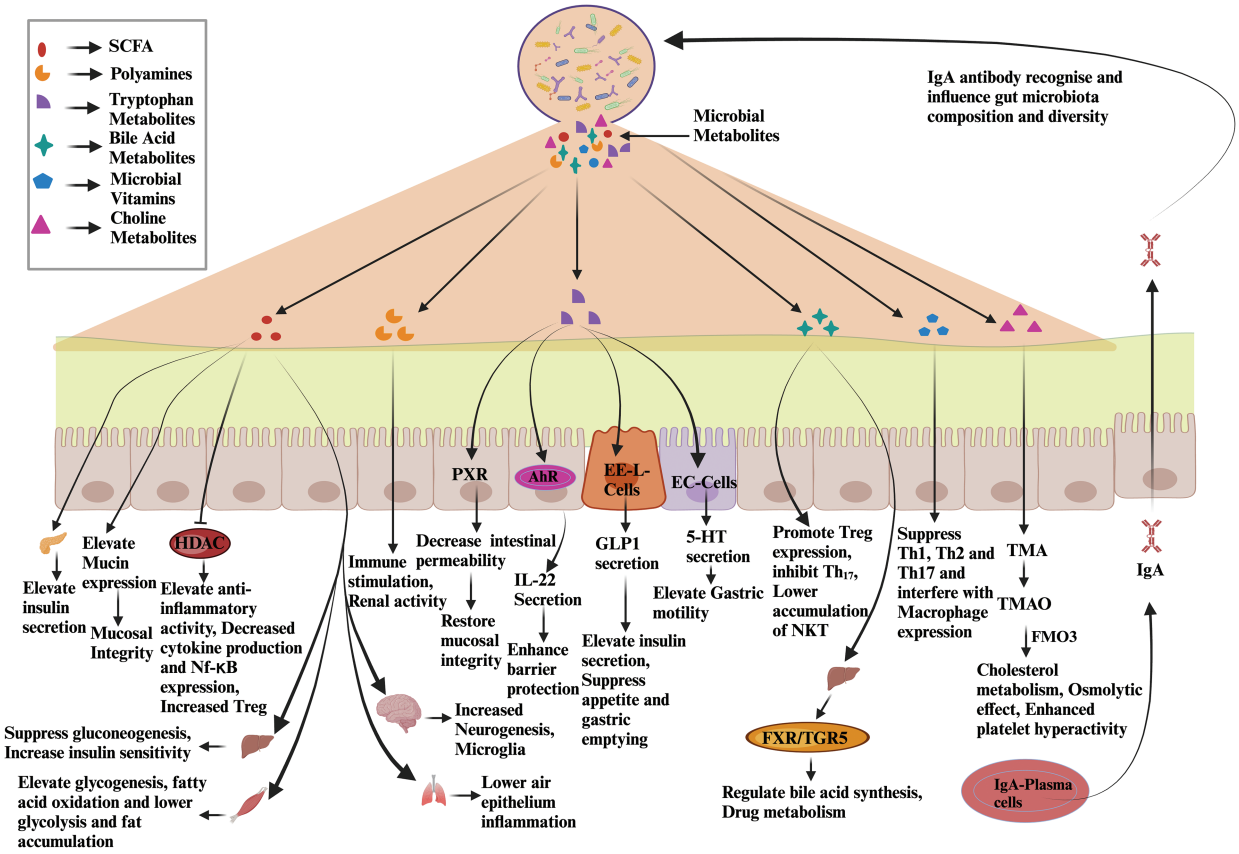

FIGURE 1. Gut microbiota-derived metabolites influence host physiology. Gut microbiota metabolizes the ingested food particles and produces metabolites like SCFAs, tryptophan metabolites, bile acid metabolites, choline metabolites, and microbial vitamins. These metabolites influence the host physiology by regulating various signaling cascades. Abbreviations: HDAC: Histone deacetylase, Treg: Regulatory T cells, PXR: Pregnane X receptor, AhR: Aryl hydrocarbon receptor, IL-22: Interleukin 22, EE-L-Cells: Enteroendocrine cells, GLP1: Glucagon-like peptide 1, EC-cells: Enterochromaffin-like, 5HT: 5 Hydroxy tryptamine, NKT: Natural killer T cells, FXR: Farnesoid X receptor, TGR5: Takeda G protein-coupled receptor 5, Th1,2: Type 1 T helper cells, Type 2 T helper cells, Th17: T helper 17, TMA: Trimethylamine, TMAO: Trimethylamine N-oxide, FMO3: Flavin-containing dimethylaniline monooxygenase 3, IgA: Immunoglobulin A.

interactions alter microbiota dysbiosis, causing chronic inflammation [50]. A leaky gut and inflammation are the primary culprits for the onset of diseases. A leaky gut exposes microbes and microbial antigens to the host's immune system, disturbing host-microbe interactions [51]. Intestinal epithelial integrity is disturbed by tumor necrosis factor alpha (TNFα)-dependent nuclear factor kappa B (NF-κB) [52]. NF-κB stimulates the myosin light chain kinase (MLCK) promoter, which leads to cytoskeletal contraction and the opening of tight junctions in the intestinal epithelium cells [53]. The compromised barrier integrity allows the exposure of microbial antigens to TLRs to activate the innate immune system [54]. It subsequently creates a pro-inflammatory environment by targeting the immune cells such as macrophages, dendritic cells, and Th17 cells [54]. The TNFα-induced NF-κB pathway significantly impacts inflammatory bowel disease (IBD) pathogenesis [55] (Fig. 2).

The dysregulation of signaling by NF-κB leads to uncontrolled inflammation and altered immune responses in gastric diseases [52]. Similarly, IL-1β plays a crucial role in intestinal inflammation, particularly in Inflammatory Bowel Disease (IBD), such as Crohn's disease [59]. In previous studies, IL-1β, produced by NOD-like receptor protein 3 (NLRP3) inflammasome, contributes to the provocation of inflammation in IBD. The NLRP3 inflammasome activates IL-1β, and an exaggerated level of its activity can instigate intestinal inflammation [60]. In the case of active Ulcerative Colitis (UC) and Crohn's Disease (CD), NLRP3 and IL-1β are upregulated, and the spatial localization of these entities suggests the occurrence of inflammasome-independent processing of IL-1β [60]. IL-1β can suppress the expression of PDZ domain-containing scaffolding protein1 (PDZK1), which regulates intestinal receptors and transporters, by activating NF-κB [61]. Notably, IL-1β also triggers the activation of NF-κB, which subsequently represses gastrin, a pivotal hormonal regulator of acid secretion within the gastrointestinal tract [62]. IL-1β-dependent NF-κB signaling is implicated in intestinal inflammation and regulating diverse gastrointestinal processes, encompassing cytokine production [63]. The IL6-dependent STAT3 activation has also been involved in developing gastric diseases [64]. Moreover, IL-6 has been identified as a necessary target for therapeutic intervention in IBD due to its enhanced expression in the serum and mucosa of patients with active disease [65]. The IL-6/gp130/STAT3 signaling pathway plays a significant role in preserving the integrity of the intestinal barrier to counteract bacterial invasion [66]. However, the dysregulation of IL-6/STAT3 signaling, characterized by an imbalance between STAT3 and suppressor of cytokine

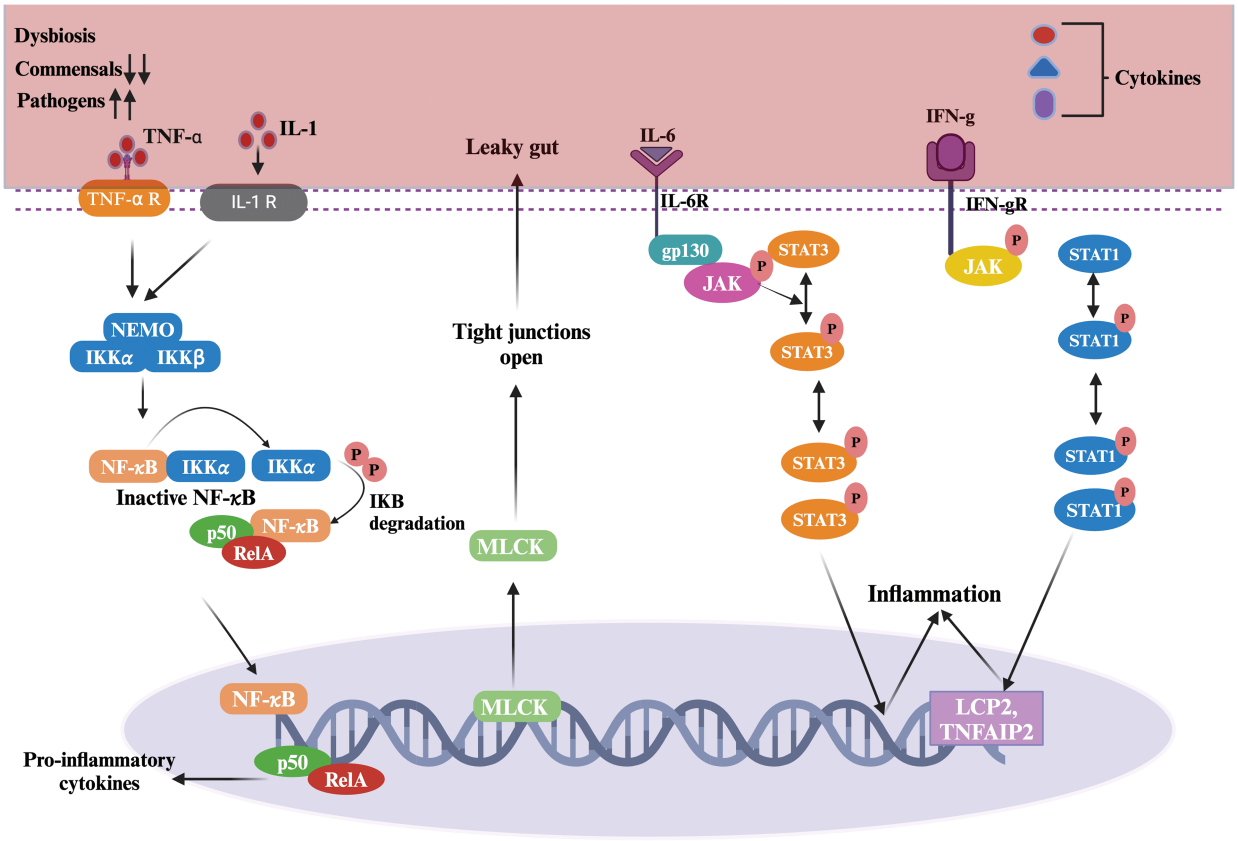

FIGURE 2. Host-microbe interactions during microbiota dysbiosis associated with human illnesses. The host's inflammatory pathways are activated in response to antigen stimulation. TNFα and IL-1 act binds to TNF-α-Receptor and IL-1 Receptor, respectively. TNFα binding to its receptors activates the IKK complex, activating NF-κB. IKK complex phosphorylates IκBα, leading to its degradation. Once IκBα is degraded, NF-κB is translocated to the nucleus. In the nucleus, NF-κB binds to the MLCK gene to regulate target genes, contract tight junction proteins, and promote leaky gut. Similarly, other inflammatory factors, IL-6, and IFN-γ, enhance inflammation by the JAK-STAT pathway. IFN-γ-STAT1 pathway activates LCP2 and TNFAIP2, which induce chronic inflammation. The IL-6 pathway is important for immune response, inflammation, and cell survival in the gut. The binding of IL-6 to its receptor complex activates JAKs associated with gp130. JAKs phosphorylate specific tyrosine residues on gp130, creating docking sites for STAT proteins. Phosphorylated STATs dimerize and translocate to the nucleus. STAT dimers bind to particular DNA sequences and regulate the transcription of target genes. IL-6/STAT signaling promotes the survival and proliferation of intestinal epithelial cells, maintains mucosal barrier integrity, and modulates immune cell responses. Excessive or prolonged IL-6/STAT signaling contributes to chronic inflammation and is involved in the pathology of IBD. IFN-γ binds to its receptor, and downstream activates JAKs, which further phosphorylate and activate STAT-1. STAT-1 dimer translocates to the nucleus and binds to LCP2 which contributes to T-cell activation, and TNFAIP2, which enhances inflammation [56–58]. Abbreviations: IL-1: Interleukin-1, IKK: Inhibitor of nuclear factor kappa B kinase, IFN-γ: Interferon-gamma, JAK-STAT: Janus kinase-Signal transducers and activators of ttranscription, LCP2: Lymphocyte cytosolic protein 2, TNFAIP2: Tumor Necrosis Factor, Alpha-Induced Protein 2, gp130: glycoprotein 130, RelA: v-rel avian reticuloendotheliosis viral oncogene homolog A.

signaling 3 (SOCS3), has been observed in IBD-associated dysplasia, indicating a potential disruption in the negative regulation of SOCS3 [66]. The involvement of IFN-γ and STAT1 can be observed in IBD. The association between STAT1, Histone acetyltransferase 300 (EP300), and Histone 3 lysine 27 acetylation (H3K27ac) contributes to the development and progression of Inflammatory Bowel Disease (IBD) [58]. Conclusively, NF-κB-induced inflammasome, oxidative burst, disruption of intestinal epithelial integrity, and intestinal leakage are prominent molecular changes during the onset of various microbiota dysbiosis-associated disorders [67]. These cellular changes have to be reversed to overcome microbiota dysbiosis-associated disorders. Accordingly, multiple therapies are being developed targeting these molecular markers.

Human gut microbiota continuously cross-talk with other organs through the gut- the respective organ axis (Fig. 3) [68]. Hereby, cellular changes affect intestinal physiology and alter the physiology of other organs like the brain, kidney, heart, liver, lungs, and skin [69,70]. The gut-organ axis works as a medium to exchange microbial metabolites between the gut and that organ. Gut microbiota dysbiosis has been reported in various organ-associated diseases [71]. This axis may be the path to dysbiosis-related disease flare-ups [72]. Hereby, any therapy and molecule targeting molecular markers of gut microbiota dysbiosis-associated diseases would help regain healthy physiology in other organs.

Plant Metabolites and Host-Microbe Interactions

Plant metabolites play a significant role in the interactions between hosts and microorganisms and in the overall well-being of humans [73]. These metabolites, namely

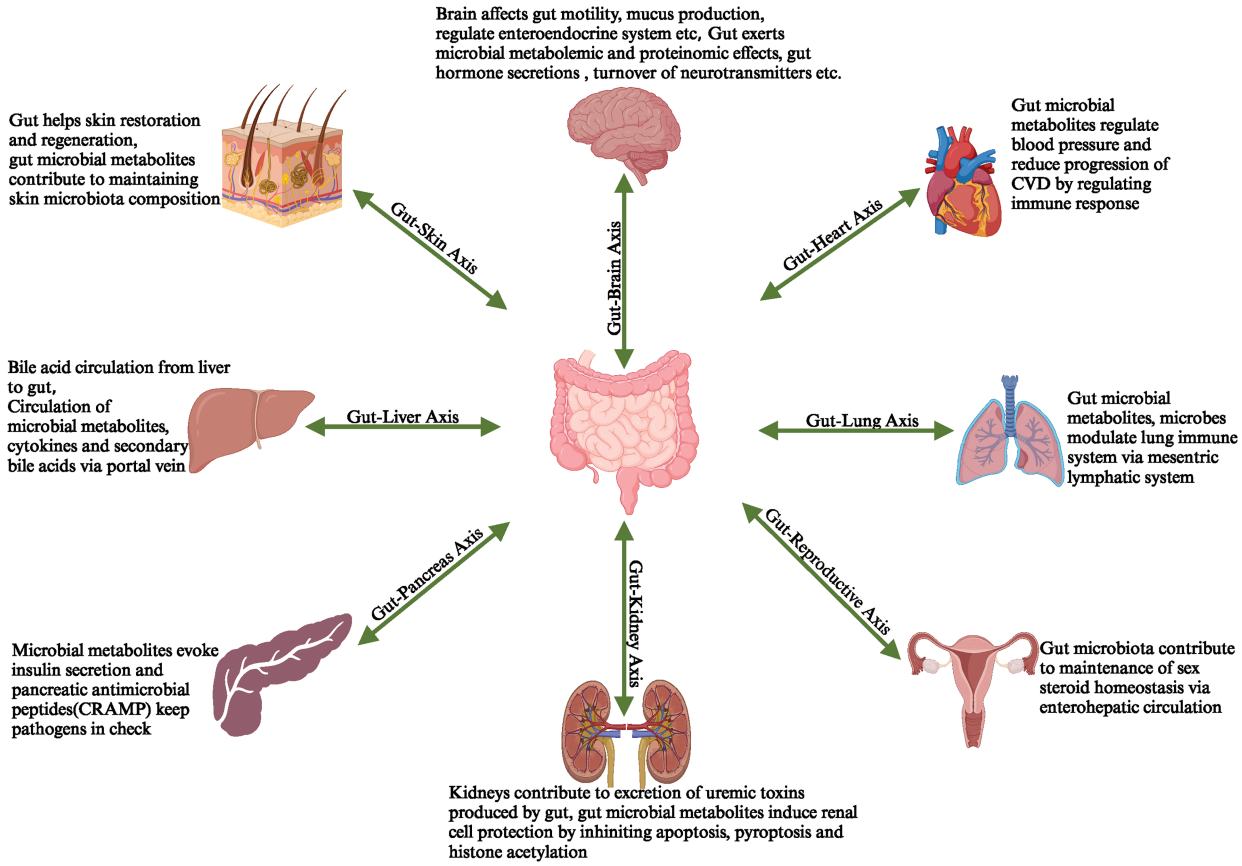

FIGURE 3. Gut microbiota-produced metabolites are exchanged between the gut and organs, which leads to the formation of the Gut-organ Axis.

phytochemicals and flavonoids, are inherent compounds in food constituents and possess diverse properties promoting human health [74]. They can be directly absorbed into the bloodstream and modulate the gut microbiota, subsequently impacting the host's health [75]. The gut microbiota enhances the bioactivity of phytochemicals [76]. Moreover, it generates metabolites from phytochemicals that exhibit therapeutic effects on human ailments [76]. Moreover, bioactive substances sourced from plants can impact the variety of gut bacteria and improve the intestinal barrier integrity, aiding in managing and preventing various illnesses [75].

The significant contribution of plant-derived metabolites to host-microbe interactions is their ability to modulate the immune response and modify the integrity of the gut barrier [77]. These metabolites and their bioactive forms invoke the immune response by stimulating numerous immune cells and regulating cytokines [77]. Similarly, plant metabolites influence the integrity of the gut barrier by modulating the functionality of tight junction proteins, impacting gut microbial diversity, promoting mucin secretion, and alleviating oxidative stress [78].

Plant Metabolites and Gut Microbiota Immune Axis

A balance between pro- and anti-inflammatory mediators in the gut is necessary to preserve the intestinal epithelial barrier [79]. According to a study, immune cells in the bloodstream can penetrate the mucosa and release a range of inflammatory mediators that intensify the gut's immunological response [80]. Therefore, a successful treatment approach for gastrointestinal disorders is to prevent the invasion of immune cells and inflammatory factors, restoring the integrity of the intestinal partition [81]. Phytochemicals like resveratrol, quercetin, colchicine, genistein, capsaicin, and epigallocatechin-3-gallate can modulate immunity and control critical molecular and cellular interactions [82]. They target several immune response signaling pathways, such as the TNF-α/NF-κB, IL-1/NF-κB, IFN-γ/JAK/STAT, and IL-6/JAK-STAT pathways [83]. Ursolic acid, gingerol, flavopiridol, curcumin, and green tea catechins can inhibit one or more steps of the NF-κB signaling cascade and act as immunomodulatory compounds [84–87]. These phytochemicals help manage cytokine storms since pharmacological profiling reveals strong NF-κB signaling pathway inhibitions [88]. By promoting the immune system's health and regulating immunological responses, phytochemicals also help establish healthy host-microbiota interactions. They can balance the immune system and control the release of pro-inflammatory cytokines, essential for overcoming gut microbiota-associated disorders [89].

Quercetin inhibits the nuclear translocation of the NF-κB receptors' p50 and p65 subunits, lowering pro-inflammatory gene production [90]. By preventing Iκ-Bα degradation and p65 nuclear translocation, quercetin also reduced the gene expression and production of IL-1β, IL-6, IL-8, and TNF-α in human mast cells [91]. Various plant compounds inhibit

the host NLRP3-mediated inflammation by inhibiting the intermediate effector molecules of the pathway [92]. Apigenin inhibits the production of pro-inflammatory cytokines in lipopolysaccharide (LPS)-induced T cell human leukemia virus positive-1 (THP-1) macrophages, such as TNF-α, IL-1β, and IL-6. When exposed to LPS, apigenin reduces NF-κB activation. Still, it does not affect NLRP3 mRNA or protein levels or apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) protein levels [93]. Nevertheless, apigenin prevents the development of ASC specks, protein aggregates necessary for the NLRP3 inflammasome to be activated. This implies that apigenin inhibits NLRP3-mediated inflammation by directly targeting ASC [94]. Apigenin can prevent the phosphorylation of two tyrosine kinases that are involved in the phosphorylation of ASC: protein tyrosine kinase 2 (Pyk2) and spleen tyrosine kinase (Syk) [95]. Additionally, apigenin was shown to block IL-1β production mediated by absent in melanoma 2 protein (AIM2), another kind of inflammasome, but not NOD-like receptor family CARD domain containing 4 (NLRC4)-mediated production [96]. This suggests that apigenin inhibits a variety of inflammasome types, indicating that it is a non-selective inflammasome inhibitor. Another phytochemical cardamonin inhibits the NF-κB pathway, a signaling system implicated in inflammation, in RAW 264.7 cells, an immunological cell type [97]. This inhibition occurs by suppressing the inflammatory chemicals prostaglandin-E2 and nitric oxide (NO) [98]. Suppression of these molecules reduces phosphorylation and degradation of Iκ-Bα, a protein that stimulates the NF-κB pathway [99]. The capacity of cardamonin to upregulate the Aryl hydrocarbon receptor (AhR)/Nuclear factor erythroid 2-related factor 2 (Nrf2)/NAD(P)H quinone dehydrogenase (NQO1) signaling pathway, which is known to regulate the NLRP3 inflammasome adversely, is another possible mode of action [94]. Cardamonin has been extensively researched about cancer, but it has also been explored in rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and other disorders [94,100]. Research has shown that the main bioactive component of *Polygonimultiflori Radix* (PMR) water extract, 2,3,5,4′-tetrahydroxystilbene-2-O-β-D-glucoside (TSG), may increase the level of the anti-inflammatory cytokine IL-10 and reduce the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6 [101]. Similarly, as reported, aloe vera administration increased the production of IL-10 while suppressing the expression of pro-inflammatory colonic mediators. This inflammation regulatory role of aloe vera might be attributed to its metabolites, including aloins, emodin, and chrysophanol [102,103]. The traditional Chinese medicine formula Shen-Ling-Bai-Zhu-San (SLBZS), constituted of panaxadiol, disogenin ginsenosides Rg1, neferine, atractylenolide I, II, III, isoliquiritigenin and liquiritigenin, platycodin D. These metabolites may lessen colonic damage, enhance body weight loss brought on by sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS), and reduce the disease activity index (DAI) score [104]. *Jasoniaglutinosa* (L.) DC. (JGD), a traditional herbal remedy referred as rock tea [105], was found to be rich in phytochemicals like pigments (xanthophyll, lutein, β-carotene, chlorophyll b, chlorophyll a, pheophytin a, phenolic substances (hydroxycinnamic acids caffeoylquinic acid, etc.) and flavanols (quercetin-3-O-galactoside) [106]). The investigation revealed that rock tea metabolites had a protective impact on the intestinal barrier and significantly decreased DSS-induced pathological changes.

Pro-inflammatory cytokines such as TNF-α and IL-6 may be produced less often by these components of rock tea [105,106]. Conclusively, plant metabolites hold the potential to control the function of the intestinal barrier and influence the course of the illness by regulating the host inflammatory response essential for equilibrated host-microbiota interactions for good health (Fig. 4).

Plant Metabolites and Gut-Barrier Integrity

The intestinal barrier is essential to safeguard stratified gut microbiota in intestinal mucosa and host-microbiota crosstalk [107]. The gut epithelium, the mucus layer, and the microbiota collectively constitute the barrier [108]. These barriers efficiently seal the gaps between neighboring cells [109]. The epithelium's goblet cells secrete mucin, which forms a mucus coating that prevents potentially pathogenic bacteria from making immediate contact with the epithelium [110]. The commensal microbiota plays a crucial role in host protection by impeding the proliferation of pathogenic organisms through nutritional competition [24]. Furthermore, SCFAs produced by the gut microbiota promote the proliferation of epithelial cells [111]. The biochemical barrier encompasses various bioactive molecules, including gastric acid, regenerating family member 3 gamma (Reg3γ), defensins, secretory immunoglobulin A (sIgA), and antimicrobial peptides generated by intestinal Paneth cells [112]. These bioactive compounds can alter the microbiota's structure or directly aid in eradicating pathogenic bacteria [113]. The lamina propria of the gut contains a variety of immune cells that make up another part of the biochemical barrier [80]. These cells limit infections by regulating normal immune responses [114]. Disrupted gut barrier integrity has been reported in various gastrointestinal diseases such as IBD, UC, colorectal cancer, etc. [55]. Plant-derived metabolites like berberine, curcumin, lycopene, aloin, polysaccharides, etc., contribute to maintaining gut barrier integrity by modulating tight junction proteins, stimulating mucin production, or altering microbiota diversity [115]. The tight junctions, protein complexes located at the interface connecting cells, serve a vital role in modulating the epithelium's permeability and structure [116]. Underexpression of tight junction proteins is already observed in UC patients, animals with experimental colitis, and during the onset of IBD [117]. Recent studies have discovered that various traditional medicinal concoctions can improve the integrity of the intestinal barrier function by controlling the expression of tight junction proteins, which can reduce colonic inflammatory situations [107]. In Caco-2 cells, the administration of Dahuang Mudan decoction (DMD), a popular medication for intestinal disorders, markedly elevated the expression of Claudin-1,

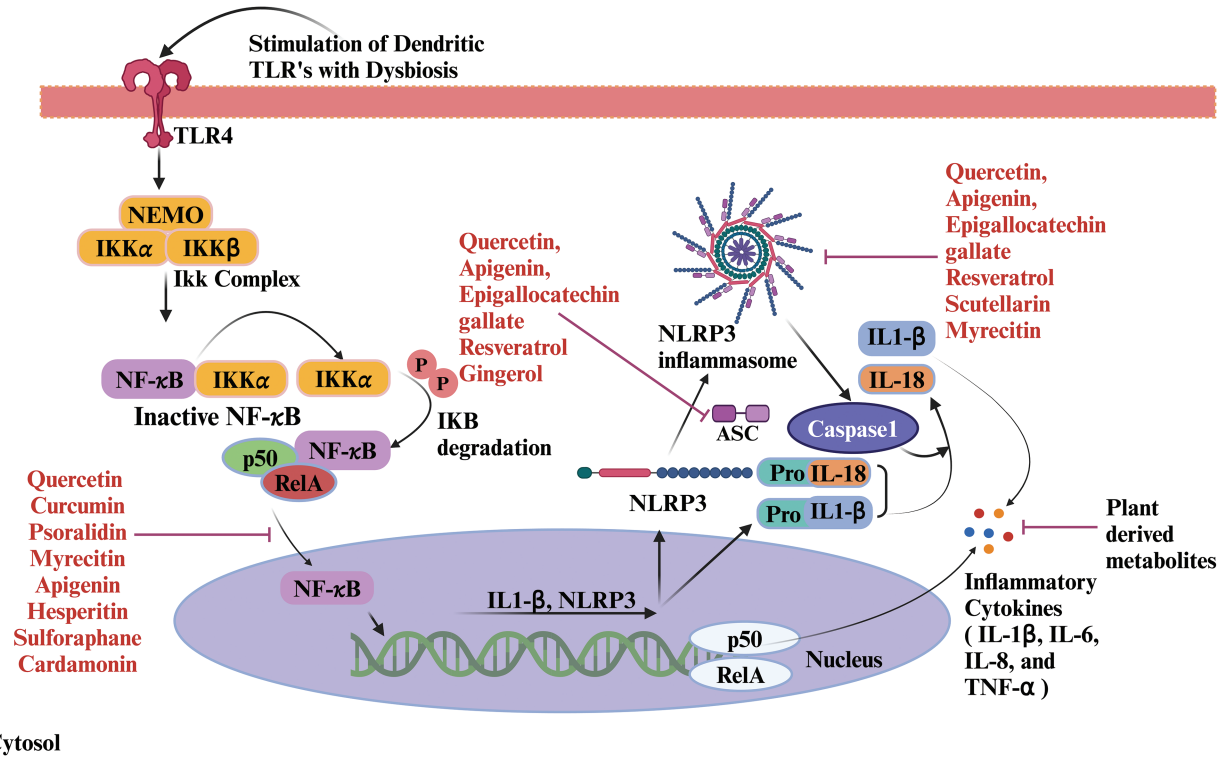

FIGURE 4. Role of plant metabolites on host immunological response. Gut dysbiosis stimulates TLRs of dendritic cells and inflammatory pathways. TLRs start signaling pathways that activate the NF-κB pathway downstream. TLR signaling induces IκB phosphorylation and degradation, allowing NF-κB to translocate to the nucleus along with p50/RelA. In the nucleus, NF-κB promotes the transcription of inflammatory cytokines. The assembly of ASC specks activates the NLRP3 inflammasome. The assembly of the NLRP3 inflammasome activates the caspase-1. Caspase-1 processes pro-inflammatory cytokines into their active forms. The secretion of IL-1β and IL-18 enhances the inflammatory response. Plant-derived metabolites act as immunomodulators by inhibiting the inflammatory pathways at different stages. Abbreviations: TLR4: Toll-like receptor 4, NEMO: NF-κB essential modulator, IKKα: Inhibitor of nuclear factor kappa B kinase alpha subunit, IKKβ: Inhibitor of nuclear factor kappa B kinase beta subunit, RelA: v-rel avian reticuloendotheliosis viral oncogene homolog A, NLRP 3: NOD-like receptor protein 3, ASC: Apoptosis-associated speck-like protein containing a caspase recruitment domain, IL: Interleukin.

occluding, and ZO-1 [118]. The primary metabolites of DMD belong to anthraquinones such as emodin, aloe-emodin, rhein, paeoniflorin, and amygdalin [115]. Additionally, it lowers the ratio of natural cytotoxicity receptor (NCR) innate lymphoid cell-(ILC3) and raises the fraction of IL-22 + ILC3 and NCR + ILC3 [118]. *Bryophyllum pinnatum* (Lamarck) Leaf metabolites kaempferol 3-O-α-L-arabinopyranosyl-(1→2)-α-L-rhamnopyranoside, quercetin 3-O-α-L-arabinopyranosyl-(1→2)-α-L-rhamnopyranoside, and quercetin-3-O-rhamnopyranoside have been shown the anti-UC effects, at least in part due to its regulation of ZO-1 [119]. According to a different study, TSG, an active component of *Polygonimultiflori radix* (PMR) aqueous extract, may increase the expression of tight junction proteins like occludin and ZO-1, thereby restoring the structure of the intestinal epithelial barrier [101]. In DSS-induced colitis, polysaccharides from *Scutellariabaicalensis georgi* (SBG) reduced pathological damage to the colon. It improved the integrity of the intestinal barrier by upregulating the expression of tight junction proteins such as claudin-5, ZO-1, and occludin [120]. On the other hand, the precise roles of the chemical components in some conventional decoctions or compounds that occur naturally are still unidentified. Further studies addressing these issues may facilitate the development of new drugs for treating UC by regulating tight junction proteins. Besides tight junction protein, mucin proteins are also affected in intestinal disorders. Mucin deficiency is found to be associated with the onset of infantile IBD [121]. A lack of anterior gradient 2 (AGR2), a disulfide isomerase involved in mucin processing, severely affects the mucus barrier [121,122]. By upregulating phosphorylated Protein kinase C (p-PKC) and phosphorylated extracellular signal-regulated kinase (p-ERK) and downregulating phosphorylated phosphoinositide 3-Kinase (p-PI3K) and phosphorylated- A serine-threonine kinase (p-AKT), aloe vera promoted the production of mucins [102]. Anemone chinensis Bunge (ACB) constituents enhance the production of mucin, specifically mucin-2 and mucin-3A [123]. Furthermore, a correlation between the beneficial effects of *Bryophyllum pinnatum* (Lamarck) Leaf extract on UC and its ability to stimulate MUC-3 expression has been observed [109]. White Ginseng constituting ginsenosides (Ra1, Rb1, Rb2, Rc, Rh2, Re, Rg1, Rg, vina ginsenoside R2, pseudoginsenoside F11 and majonoside R1), flavonoids, volatile oil has also shown the potential to significantly increase the mRNA expression of Muc2 [124], a prominent mucin found in the intestines of rats. This augmentation can effectively strengthen the intestinal barrier function and improve the gut ecosystem [125].

Plant Metabolites and Microbiota Interactions

Gut microbiota and plant extract, enriched with metabolites or phytochemicals, have cyclic interactions [126]. Exposure of plant phytochemicals to gut microbiota allows their metabolic transformation into different metabolites with improved bioavailability [127]. Simultaneously, plant extracts or phytochemicals modulate the gut microbiota in a variety of ways, including governing the ratio of beneficial to pathogenic bacteria, restoring the diversity of the gut microbiota, enhancing the function of the intestinal barrier, and controlling the metabolites of the gut microbiota (Fig. 5) [128].

Though the mechanism behind plant modulation of gut microbes has not been fully discovered, it can be attributed to the prebiotic, anti-inflammatory, anti-microbial, and antioxidant characteristics of plant constituents, which create a favorable environment for beneficial microbiota flourishing [118,129] (Fig. 5). Medicinal decoctions, loaded with different metabolites from various plants, which work synergistically in a decoction, have been found to alleviate dysbiosis and restore gut microbiota homeostasis [130]. The TSG, a bioactive component of *Polygoni multiflori* Radix (PMR), increases the abundances of Firmicutes and Bacteroidetes [101]. The bioactive ingredients of Rhubarb, Rhein considerably decreased uric acid which acts as a colonic inflammatory substance [131]. Moreover, Rhein may modify purine metabolism and cause alterations in the gut microbiota's makeup, both sufficient to reverse the colon damage caused by DSS [131]. The primary metabolites of Jiawei Gegen Qinlian Decoction (JGQD), puerarin, magnolol, baicalein, berberine, and glycyrrhiic acid may cause *Escherichia-Shigella* to decline and *Akkermansia* and *Romboutsia* to grow [132]. In addition to these modifications, the administration of polysaccharide SP2-1 altered the microflora's composition by considerably increasing the amounts of *Firmicutes, Bifidobacterium, Lactobacillus,* and *Roseburia* and reducing the quantities of *Bacteroides, Proteobacteria*, and *Staphylococcus* in the gut [133].

Plant-derived metabolites also serve as prebiotics to enhance the diversity and composition of gut microbiota [130]. The polysaccharides of *Taraxacum officinale*, commonly known as dandelion, have been found to exert the prebiotic effect by enhancing the abundance of *Bifidobacterium*, *Olsenella*, and *Dialister* [134]. Similarly, another medicinal plant, i.e., Garlic, contains allicin, inulin, and fructooligosaccharides, enhances the *Bifidobacteria, Lactbacillus acidophillus* and suppresses the *Clostridia* species [135]. The prebiotic properties of plants can be attributed to the high fiber content such as inulin which is digested slowly by gut microbiota and leads to fermentation [136]. Plant metabolites like SCFA also serve as energy sources and are generally used as markers for prebiotic activity [137]. For example, the administration of Huang-Lian Jie-du decoction increased the diversity of gut microbiota, an augmentation in the abundance of *Lactobacillus*, and a reduction in *Firmicutes* [138]. Furthermore, the administration of Radix Astragali-Radix Salviae Miltiorrhizae increased the levels of probiotics, such as *Lactobacillus* and *Bifidobacterium* [139]. These strains of beneficial bacteria were found to be closely associated with

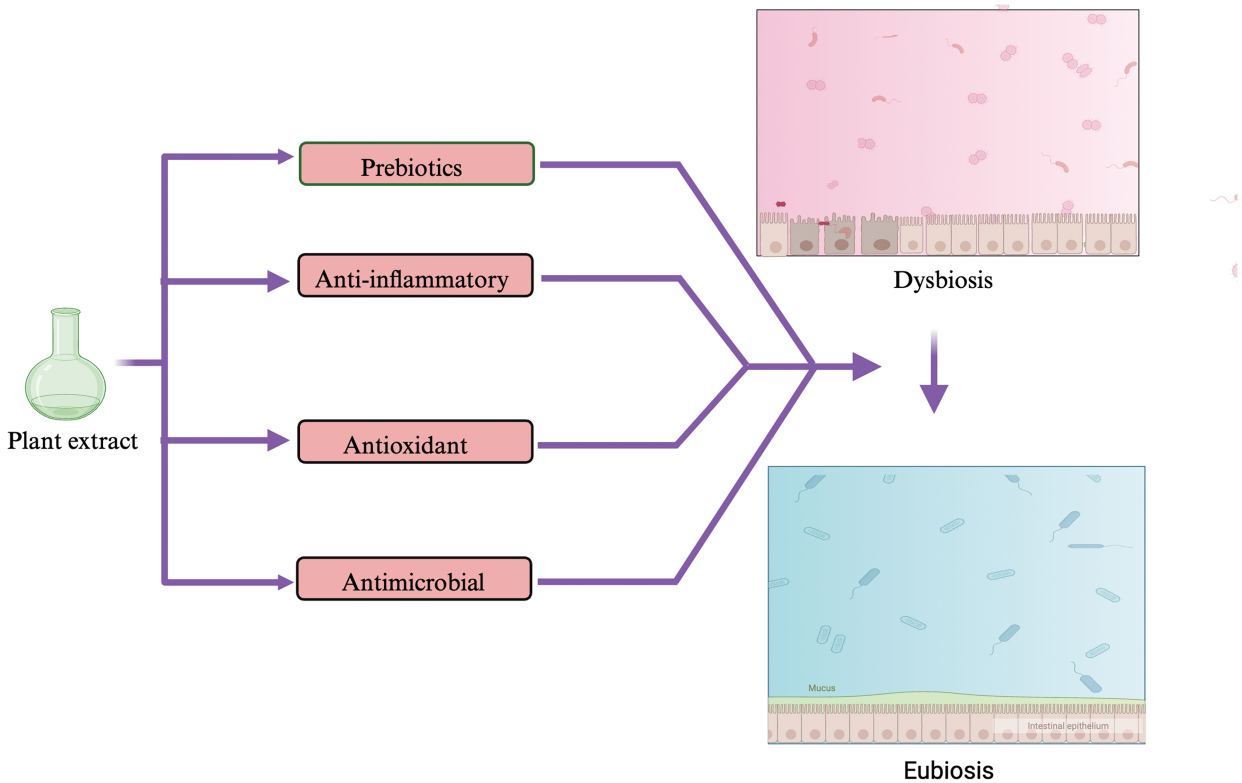

FIGURE 5. Medicinal plants possess prebiotic, anti-inflammatory, antioxidant, and antimicrobial properties, which help in the restoration of beneficial gut bacteria and restoration of eubiotic conditions in the gut.

decreased blood pressure and other hypertension-related symptoms [140,141]. The influence of plant extracts and derived metabolites on microbes has also been noted in mental disorders related to the gut-brain axis [142]. Curcumin, a well-known phytochemical, has been discovered to diminish the presence of *Prevotella*, *Coriobacterales*, and *Ruminococcus*, which are significant disease-related microbes [143]. In an animal model of Alzheimer's disease, the ratio of *Firmicutes* to *Bacteroidetes* increased, the abundance of anaerobic and *Helicobacter* decreased [144], and an enhancement in cognitive function was observed following the administration of curcumin [145]. Humulones and lupulones present in the female flowers of *Humulus lupulus* L. (commonly known as hop) are utilized as herbal remedies for treating conditions such as anxiety, mood disorders, and sleep disturbances [146].

Inflammation plays a pivotal role in developing dysfunction in the epithelial layer. Disruption of the epithelial barrier allows harmful antigens to pass through, further elevating local inflammation [147]. The inflammatory response recruits immune cells, such as macrophages, to generate reactive oxygen species (ROS) and induce oxidative stress [148]. Consequently, gut inflammation and oxidative stress are interconnected processes [149]. Inflammatory cytokines hinder the proper functioning of the epithelial barrier by weakening the tight junctions between the epithelial cells [150]. These alterations ultimately lead to chronic gut inflammation, as observed in patients suffering from IBD [151]. This chronic inflammation may result in mucosal erosion and ulceration [151]. Hence, the combination of oxidative stress, inflammation, and impaired gut epithelial barrier contributes to dysbiotic conditions [152]. However, introducing antioxidants derived from plants can effectively suppress oxidative stress and inflammation in the mucosal layer of the gut, thereby improving overall gut health [153]. By modulating effector molecules, including superoxide radicals, arachidonate 5-lipoxygenase (5-LOX), inducible nitric oxide synthase (iNOS), nitric oxide (NO), and Cyclooxygenase 2 (COX2), another mechanism implicated in barrier homeostasis maintenance is connected to a decrease in oxidative stress [154]. Various plant-derived metabolites, such as astaxanthin, resveratrol, curcumin, naringenin, quercetin, etc., have been reported to act as antioxidants, thus alleviating oxidative stress [155]. Previous investigations have noted that many plant-derived metabolites like β-carotene enhance the expression of antioxidant enzymes, diminish oxidative byproducts, and enhance the functionality of the gut epithelial barrier (Fig. 6) [156].

Another metabolite, lycopene consumption, shields the intestinal epithelium from deoxynivalenol-induced oxidative stress [157]. The antioxidant enzyme Plasma glutathione peroxidase (GSH-Px) and the antioxidant capacity of plasma experienced a remarkable increase in the colon of colitis-afflicted mice supplemented with the antioxidant-rich Lacto-wolfberry [158]. These advantages primarily arise from the anti-oxidative and anti-inflammatory properties of the ingested compounds [153]. Some phytochemicals have been shown to activate the Nrf2-driven redox pathway [159]. The Nrf2 pathway activates the ARE-dependent antioxidant enzymes [160,161]. The NF-κB activation and cytokines IL-6, IL-8, IL-1β, and TNFα have a pro-inflammatory role in ROS production [160,161]. Curcumin, a metabolite of Turmeric, has been shown to inhibit the NF-κB activation and thus alleviate the oxidative stress [162,163]. Therefore, it can be concluded that antioxidant, prebiotic, and anti-inflammatory are responsible for plant-derived metabolites' effect.

Plant Metabolites in Personalised Therapy

Personalized therapy (PT), or personalized medicine, involves customizing medical interventions for individual patients by considering their distinctive characteristics like genetics, lifestyle, and diagnostic information [164,165]. The primary goal is to deliver precise treatment to each patient by interindividual heterogeneity, apart from the conventional one-size-fits-all methodology [166]. This strategy leverages advancements in diagnostic imaging, molecular medicine, and artificial intelligence, notably deep learning algorithms such as Convolutional Neural Network (CNN) and recurrent neural network (RNN), to scrutinize patient data and suggest tailored therapies [167]. The need for PT arises due to adverse side effects of conventional medicine, such as multi-drug resistance in gut bacteria. Personalized therapy components are designed to work for a particular genetic repertoire, for example, warfarin and imatinib drugs [168,169]. PT is required to create the drug for a particular mutation, in the case of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutation, the drug Ivacaftor works for a single phenotype [170]. Personalized Therapy can detect the early signs of disease based on personal thresholds of a marker rather than on population thresholds [166]. Similarly, in the case of postoperative colorectal cancer, intake of aspirin leads to increased survival chances in patients who had a somatic mutation in the Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) gene compared to wild type [171]. The application of personalized treatment shows favorable outcomes in enhancing patient predictions and decreasing healthcare expenses [165].

Any agent that acts as a biomarker for disease and contributes to the development of therapeutics is significant for developing personalized therapy. In this scenario, the human gut microbiota linked to almost every disease can be a substantial agent with microbiome-based therapeutics [172].

The human gut microbiome is a critical factor in personalized therapeutics by impacting drug metabolism, disease development, and treatment methods, offering the potential for personalized therapies [173,174]. Various microbiome-based therapeutic strategies, including prebiotics, probiotics, antibiotics, dietary interventions, fecal microbiota transplantation (FMT), live biotherapeutics, phage therapy, and microbiome mimetics, are being investigated for disease treatment, aided by high-throughput technologies identifying microbial signatures linked to diseases like cancer and inflammatory bowel disease. Many of these techniques have been transitioned from laboratory to clinic, such as ingestible microbiomes (prebiotics,

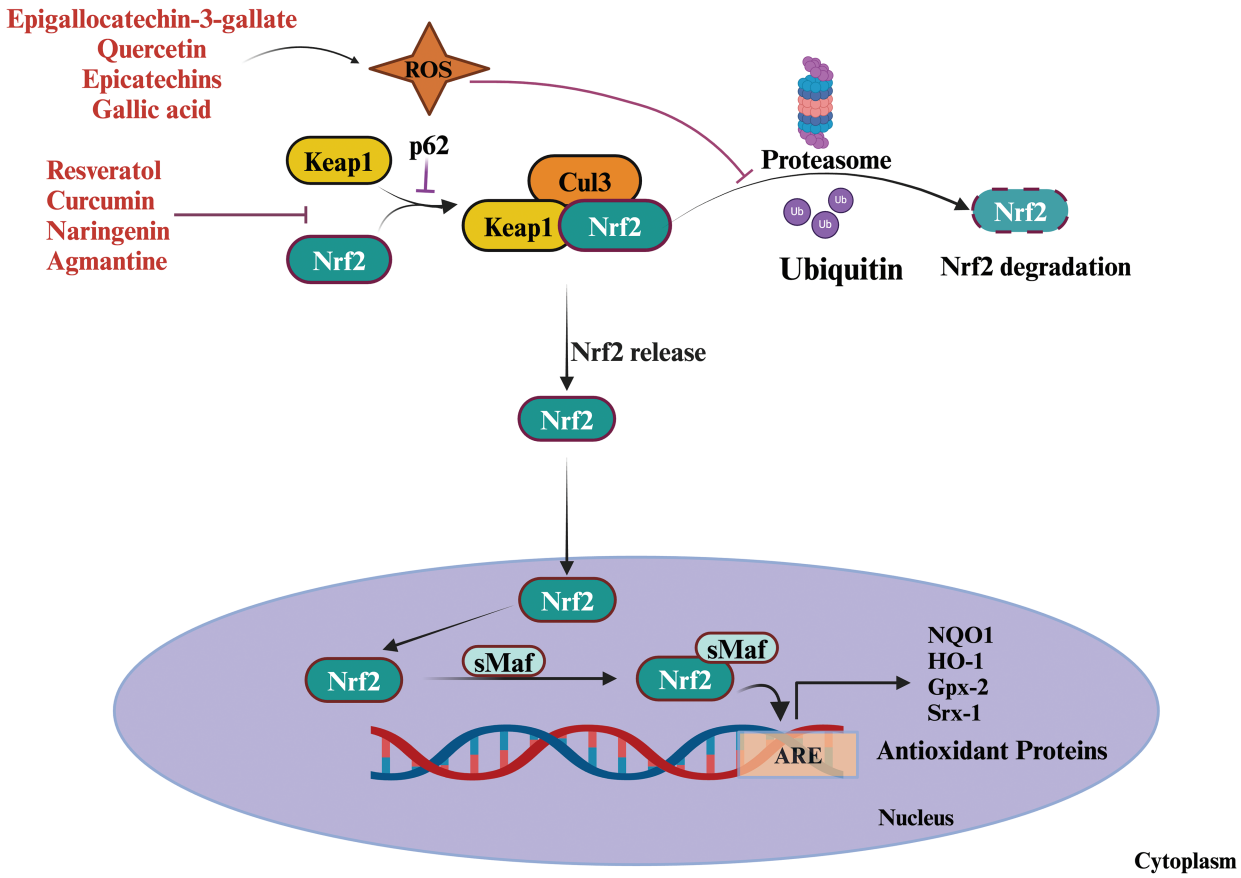

FIGURE 6. Role of plant-derived metabolites as antioxidants and pro-oxidants. Proxidants increase ROS generation and activate the Nrf2 pathway by inhibiting the proteasomal degradation of Nrf2 which subsequently produces antioxidants. Under normal circumstances, Keap 1, an oxidative stress marker, binds to Nrf2, sequestering it within the cytoplasm and marking it for ubiquitination and subsequent degradation by the proteasome. In response to oxidative stress or electrophilic compounds specific cysteine residues on Keap1 undergo modification disrupting the interaction between Keap1 and Nrf2, thereby preventing Nrf2 degradation. Consequently, Nrf2 becomes stabilized and translocates into the nucleus. Within the nucleus, Nrf2 forms a heterodimer with sMAF proteins. This Nrf2-sMAF complex subsequently binds to the (ARE) located within the promoter regions of target genes, which induces the transcriptional activation of diverse antioxidant and cytoprotective genes. These genes encode proteins such as glutathione S-transferase, heme oxygenase-1, superoxide dismutase, catalase, epigallocatechin-3-gallate (EGCG), quercetin, epicatechins, and gallic acid are involved in removing oxidative stress. While some plant-derived metabolites inhibit the interaction between Keap1 and Nrf2 by modifying the Keap1. Abbreviations : NRF2: Nuclear factor erythroid 2-related factor 2, Keap1: Kelch-like ECH-associated protein, sMAF: small musculoaponeurotic fibrosarcoma, ARE: Antioxidant Response Element, Cul 3: Cullin 3.

probiotics or postbiotics, and other medicines), which have been approved by the FDA and similar authorities [174,175]. FMT is under preclinical testing from being a strictly regulated biological agent in some countries (USA, Canada, Australia), to a medicinal product or treatment with variable regulation (UK, France, Germany, Switzerland), to no regulation (Austria, Denmark, Sweden, Finland) [176]. Thus, manipulating and understanding the gut microbiome shows potential for advancing personalized therapeutics in medicine.

In this scenario, plant metabolites can effectively influence the microbial population. Plant metabolites play a significant role in microbiome therapeutics by influencing the physiology of endophytic microbes. These metabolites, such as alkaloids, flavonoids, and polyphenols, exhibit antimicrobial properties against various pathogenic bacteria [177]. Additionally, phytochemicals interact with the gut microbiota, modulating its composition and diversity, which in turn impacts human health [79]. Long-term consumption of *Ginseng* extract rich in ginsenosides enhances the abundance of beneficial bacterial phyla like *Bifidobacterium, Allobaculum, Lactobacillus, Clostridium,* and *Parasutterella* [178]. A study reported that a combination of t-resveratrol and ε-viniferin induced changes in microbial functionality and composition, specifically an increase in *Enterobacteriales* and a decrease in *Bacteroidales* [179]. Another study investigated the effects of six stilbenoids, including resveratrol, on human fecal microbiota using an *in vitro* fermentation system. The results showed an increase in the ratio of *Bacteroidetes* to *Firmicutes* phyla, a decrease in *Clostridium genus* and *Lachnospiraceae* family strains, and an increase in the abundance of *Faecalibacterium prausnitzii* and *Ruminococcus gnavus* [180].

Some plant metabolites also function as antibacterial agents against various human pathogens; on the other hand, microbial therapeutics metabolize the plant metabolites, enhancing their bioavailability and efficacy [181]. These metabolites produced by gut microbiota alter the host's

physiology by mimicking the signaling molecules. Bacterial species like *Escherichia coli* and *Blautia* produce hydroxylated or glucuronidated metabolites of curcumin, leading to enhanced bioavailability of the compound [182]. Lignan de-glycosylation can be facilitated by *Bacteroides* and *Clostridium*, but other important taxa that may be engaged in the subsequent stages include *Eubacterium limosum, Blautia producta, Eggerthella lenta*, and *Acetobacterium dehalogenans* [183]. Catechins are broken down by gut bacteria such as *Flavonifractor, Eggerthella*, and *Eubacterium* [184] into many small phenolic metabolites are produced, such as γ-valerolactones, hydroxybenzoic acid, hydroxyhippuric acid, pyrogallol, and hydroxyphenyl propionic acid [185]. Another plant metabolite, i.e., ellagitanin is metabolized into urolithins, which regulates the inflammation via suppressing the NF-κB signaling pathway [186]. Overall, plant metabolites play a significant role in shaping microbiome therapeutics through their antimicrobial and health-promoting properties, paving the way for personalized therapy, novel drug discovery, and therapeutic interventions.

Conclusion and Future Perspective

In conclusion, investigating the impact of plant-derived metabolites on the gut microbiota represents a dynamic and evolving field with significant implications for human health. The complex interplay between the bioactive compounds found in plants and the composition of the gut microbiota highlights the potential of plant-based interventions in promoting a well-balanced and resilient microbial community within the digestive system. The observed advantages, from immune system modulation to inflammation mitigation, emphasize plant metabolites' diverse effects on gut health. As we look toward the future, there is an urgent need for comprehensive mechanistic studies to uncover the specific pathways by which plant compounds influence the gut microbiome. Furthermore, personalized nutrition strategies based on individual gut microbial profiles have the potential to revolutionize our approach to dietary recommendations. Overcoming challenges such as individual variability and standardizing research methodologies will be crucial in translating these findings into practical insights for personalized healthcare. Moreover, it is imperative to integrate sustainability considerations in plant sourcing and cultivation practices into the discussion to ensure the long-term viability of plant-based interventions. The convergence of traditional knowledge and modern scientific approaches is critical to fully realizing the potential of plant formulations in shaping the interactions between the gut microbiota and the host for optimal human health.

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