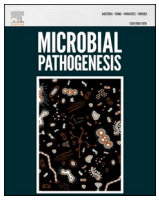
Microbial Pathogenesis 205 (2025) 107608

Contents lists available at ScienceDirect

Microbial Pathogenesis

journal homepage: www.elsevier.com/locate/micpath



A systematic review on the role of gut microbiome in inflammatory bowel disease: Spotlight on virome and plant metabolites

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ARTICLE INFO

Keywords:
IBD
Microbiome
Virome
Bacteriophage
Plant metabolites

ABSTRACT

Inflammatory bowel diseases (IBD), including ulcerative colitis and Crohn's disease, arise from various factors such as dietary, genetic, immunological, and microbiological influences. The gut microbiota plays a crucial role in the development and treatment of IBD, though the exact mechanisms remain uncertain. Current research has yet to definitively establish the beneficial effects of the microbiome on IBD. Bacteria and viruses (both prokaryotic and eukaryotic) are key components of the microbiome uniquely related to IBD. Numerous studies suggest that dysbiosis of the microbiota, including bacteria, viruses, and bacteriophages, contributes to IBD pathogenesis. Conversely, some research indicates that bacteria and bacteriophages may positively impact IBD outcomes. Additionally, plant metabolites play a crucial role in alleviating IBD due to their anti-inflammatory and microbiome-modulating properties. This systematic review discusses the role of the microbiome in IBD pathogenesis and evaluates the potential connection between plant metabolites and the microbiome in the context of IBD pathophysiology.

1. Introduction

Inflammatory bowel disease (IBD) is recognized by the World Health Organization as a chronic, recurrent intestinal condition that shows various symptoms, including intestinal bleeding, diarrhea, abdominal discomfort, and weight loss [1]. The disease is primarily divided into two types: Crohn's disease (CD) and ulcerative colitis (UC), with UC becoming increasingly prevalent worldwide [2,3]. Ulcerative colitis was first identified in 1859, while Crohn's disease was described later in 1932 [4]. The most common manifestation of Crohn's disease is intermittent inflammation that can occur any-part along the digestive tract, from the oral cavity to the rectum, and can even penetrate deeper bowel layers [5]. Conversely, UC is characterized clinically by diffuse inflammation of the mucosal surface, primarily affecting the lower colon and the rectum [6]. For a long time, IBD was predominantly documented in developed countries and was rare in developing regions [7]. As of 2019, approximately 4.9 million cases of IBD were reported globally, with the highest numbers in China and USA, accounting for 911,405 and 762,890 cases respectively (66.9 and 245.3 cases per 100,000 people) [8]. In China, the number of IBD cases was 0.45 million in 2017, and this figure is projected to rise to over 1.5 million by 2025 [9]. In Australia, according to PricewaterhouseCoopers Australia (PwC), the number of cases ranged from 75,302 to 92,571 in 2018, with a significant increasing trajectory [10].

Patients suffering from IBD face considerably higher healthcare expenses and dedicate more time to managing their health compared to patients who do not have the condition. Australia spends about AU $100 million each year for hospitalizations related to IBD, along with over AU $380 million spent on lost productivity, and an additional AU $2.7 billion on other financial and economic expenses linked to the IBD conditions [11]. Clinically, IBD is characterized according to symptoms that signify the initial acute stage of the disease, including severe diarrhea, gastrointestinal bleeding, abdominal pain, and significant loss of fluids and electrolytes [12]. The exact aetiology of IBD remains largely unknown. However, it is widely accepted that the immune system, gut microbiota, genetics, and environmental factors all play significant roles in its development. A key factor in the pathophysiology of IBD is the dysregulated intestinal immune response to the gut microbiota [13] as depicted in Fig. 1 for both normal and IBD immunological responses in the gut. Due to an imbalanced immunological response in IBD, there is

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https://doi.org/10.1016/j.micpath.2025.107608
Received 2 August 2024; Received in revised form 14 April 2025; Accepted 16 April 2025
Available online 16 April 2025

an increased secretion of cytokines and chemokines (such as IL-12, IL-23, and TNF-α) compared to the normal gut, which is responsible for increasing the permeability of the epithelial membrane [14].

Gut microbiome is a mysterious element that has a major impact on the pathology of IBD through multiple mechanisms, and several pre-clinical mouse models have suggested its potential involvement in the development and severity of the disease [15]. The gastrointestinal tracts contain over 100 trillion diverse microorganisms, encompassing viruses, bacteria, fungi, and protozoa [16]. Global initiatives focused on the microbiome have been established to understand the roles of these symbionts and their impact on human health [17]. In healthy adults, *Firmicutes* and *Bacteroidetes* are the predominant phyla in the intestines, with *Proteobacteria* and *Actinobacteria* comprising the majority of other bacteria [18]. The gut microbiota plays a crucial role in maintaining host homeostasis in a number of ways, including nutrition, immunological development, metabolic processes, and defence against pathogen [19]. Over the last ten years, inflammatory bowel disease has become one of the most researched human conditions associated with gut microbiota [19]. Numerous studies have indicated that IBD results from structural imbalances or dysbiosis in the microbiome [20]. Rather than bacteria, viruses are another crucial part of microbiome but there has been limited research focused on the virome, including eukaryotic viruses such as DNA and RNA viruses, and prokaryotic viruses like bacteriophages, in relation to inflammatory bowel disease. Norman and colleagues noted that the virome influences microbiota composition, highlighting an increase in *Caudovirales* bacteriophages in IBD compared to healthy controls, which correlates with reduced bacterial richness and diversity—two hallmarks of intestinal dysbiosis associated with IBD [21]. The mechanism of the infection between bacteriophages and bacteria have also been examined in the context of *Faecalibacterium prausnitzii*, a type of bacteria typically diminished in IBD, revealing that the decreased abundance of *F. prausnitzii* in IBD is linked to an increased proportion of *F. prausnitzii* phages in comparison to controls, indicating a higher phage-mediated destruction of *F. prausnitzii* may occur in IBD [22]. In patients with inflammatory bowel disease, *caudovirales* are probably the most enriched bacteriophages, potentially contributing to bacterial dysbiosis. Additionally, early stages of intestinal inflammation have been associated with eukaryotic viruses, specifically *Hepadnaviridae* and *Hepeviridae* [23]. Eukaryotic viruses interact not only with human host cells but also with other eukaryotic microbiota such as fungi [24]. The development and severity of IBD have been linked to changes in the gut virome structure [25,26]. Furthermore, a previous comprehensive study not only explored the dynamics of the gut virome and strategies for identifying potential disease mechanisms but also highlighted virome dysbiosis as a significant component in the onset of IBD [27].

Plant components can modify both the composition and function of microbial communities, potentially influencing the overall health and homeostasis of the host [28,29]. When plant components are consumed orally through plant-based diets, dietary supplements, or herbal medications, it is reasonable to assume that any compounds that are not absorbed in the upper gastrointestinal tract will come into contact with colonic microbe and then interactions with the gut microbiota may result in the metabolization of plant components by gut microbes and the production of metabolites with modified bioactivity profiles [30]. Plant compounds have been utilized for thousands of years to treat various common diseases in humans [31,32]. Ancient Indian scriptures also document the use of plant extracts and medicines for curing a range of human diseases. With the advancement of technology, it has become easier to isolate and identify secondary metabolites from crude plant extracts [33]. Plants and plant-derived compounds are being investigated as potential remedies for a variety of inflammatory and

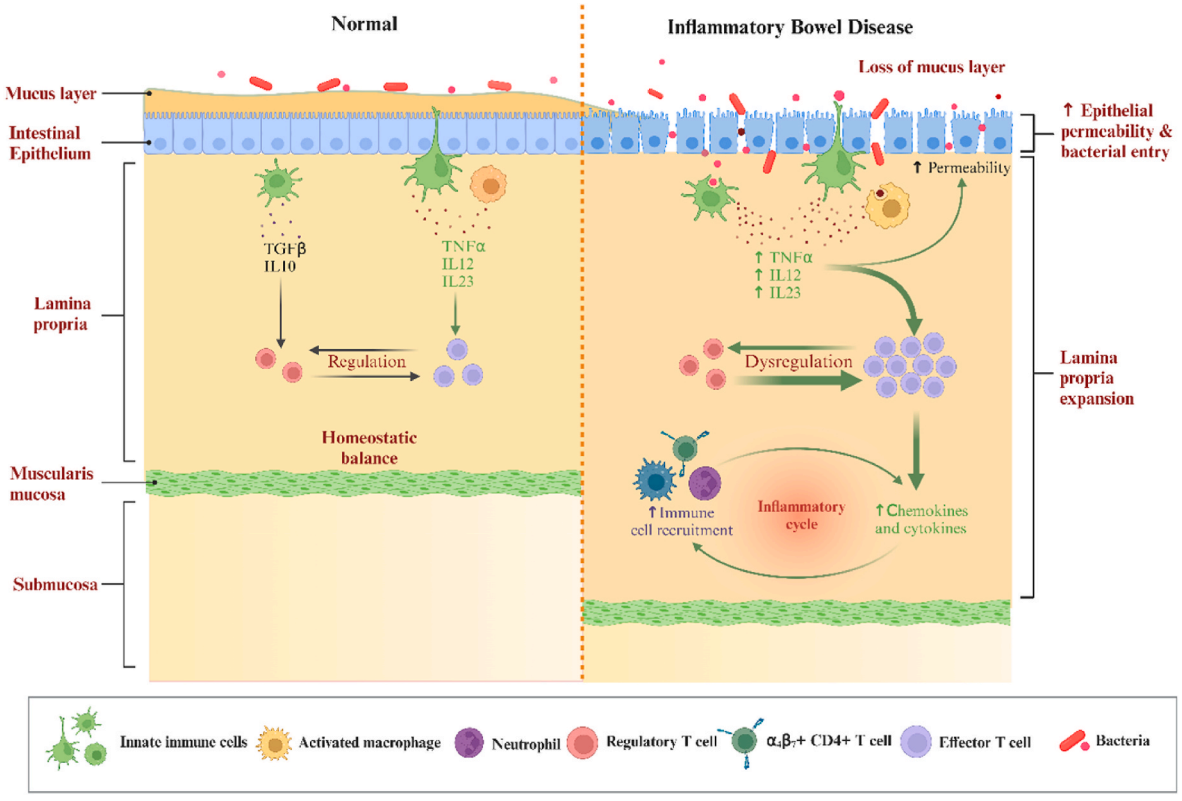


Fig. 1. Schematic on the immune responses for both normal and inflammatory bowel disease. The immune response is altered in response to gut infections in both Crohn's disease and ulcerative colitis, contributing to chronic inflammation in the gastrointestinal tract over time. During IBD, the levels of inflammatory cytokines such as TNFα, IL-12, and IL-23 increase, which in turn increases the permeability of the mucus layer. While the immune system normally protects the body from infections, abnormal activity can lead to tissue damage in the gut [Created in https://BioRender.com].

immunomodulatory conditions due to their affordability, therapeutic potential, and minimal side effects [34]. Additionally, plant metabolites exhibit properties such as lipid-lowering, anti-inflammatory, antimicrobial, antihelminthic, anticoagulant, and antidiabetic effects [35]. Several studies have demonstrated that plant-derived extracts or derivatives, such as flavonoids and phenolic compounds, exhibit anti-inflammatory activity by modulating the levels of various inflammatory mediators or cytokines, including COX-2, NO, iNOS, TNF-α, IL-6, and IL-10 [36]. Currently, there is no established cure for IBD due to the unresolved complex pathological mechanisms underlying the disease [11]. A class of drugs known as biologic agents, corticosteroids, immunosuppressants, and aminosalicylates are traditionally used in medical procedures, but these medications often have numerous side effects, making it challenging to achieve optimal therapeutic outcomes [37]. Therefore, finding a novel and safe medication is essential, particularly since many IBD patients seek alternative treatments that are perceived as safer, such as conventional plant-based medicines [38]. In this review, we have discussed the potential role of microbiome, specifically the virome and bacteriophage, in the context of IBD. Moreover, we also explored the potential interactions between plant metabolites and microbiome in the context of mitigating IBD.

2. Materials and methods

2.1. Search strategy

The data collection was conducted up until July 2024, the electronic searches included the databases MEDLINE, PubMed, Web of Science, Scopus, and Google Scholar, using the search strategy by selective keywords such as IBD, virome, bacteriophage, plant metabolites, and microbiome with the following filters: Clinical Trial, Controlled Clinical Trial, Observational Study, Review, and Humans. We also searched EMBASE, and Science Citation Index using the same terms. We integrated electronic searches with manual searches, which encompassed reviewing reference lists of relevant papers, examining conference proceedings, and engaging in correspondence with experts in the field. Initially, 303 articles were identified for review, with a few excluded due to irrelevant information. Ultimately, 179 articles were included in this review (Fig. 2).

2.2. Inclusion criteria

The inclusion criteria employed for this systematic review were as follows:

1. Studies with microbiome, plant metabolites and inflammatory bowel disease were sourced from a variety of research publications and databases.
2. Studies conducted both in vivo and in vitro, with or without the use of experimental animals, as well as those involving human subject.
3. Studies with or without elucidation of the mechanism of action.

2.3. Exclusion criteria

Following exclusion criteria were meticulously applied to ensure the rigor and relevance of this systematic review:

1. Titles and/or abstracts that did not meet the inclusion criteria, as well as duplicates of data, were excluded from the review.

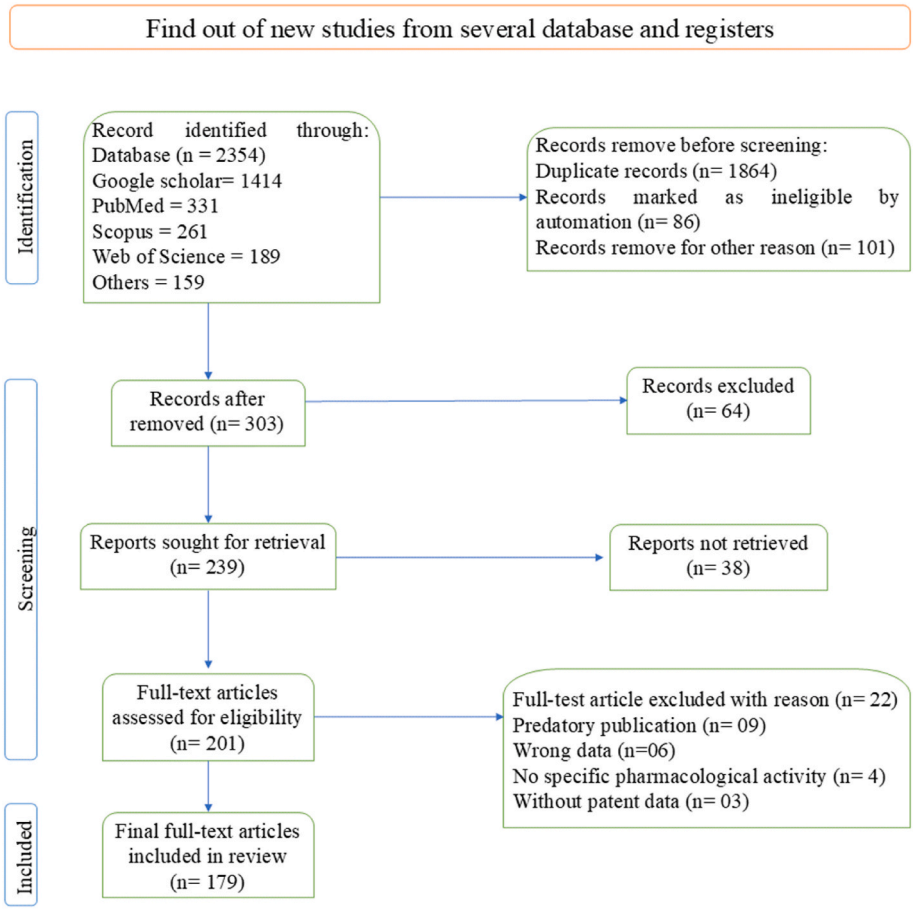


Fig. 2. PRISMA flow-diagram based on data extraction (please see supplementary file for PRISMA checklist).

2. Studies addressing the microbiome but focusing on topics that obscure or are unrelated to the current subject of interest were excluded.
3. Studies on plant metabolites that address topics obscuring or unrelated to the current subject of interest were excluded.

2.4. Findings

Among the extensive body of evidence, a selection of published articles retrieved from databases, which include screening reports on the microbiome and plant metabolites in relation to inflammatory bowel disease, is summarised in Fig. 2.

2.5. Risk of bias in individual studies

To assess the reliability of the results from the selected studies, we used the Cochrane risk-of-bias assessment criteria, specifically the RoB 2 tool version, dated 22 August 2019. This tool evaluates risk across several domains: the randomization process, deviations from intended interventions, missing outcome data, outcome measurement, selection of reported results, and other potential sources of bias. Each category comprised of questions across these domains, with responses categorized as "YES" (indicating low risk of bias, color-coded green), "NO" (indicating high risk of bias, color-coded red), or "Some Concern" (indicating uncertain risk of bias, color-coded yellow) (Fig. 3).

3. Results

3.1. Pathogenesis of IBD

The exact cause of IBD is still uncertain, numerous studies have been conducted to identify new pathogenic variables associated with IBD which are related to immune response, microbial, genetic, and environmental factors [39] as summarised in Fig. 4. Research indicates that the aetiology of IDB may be attributed to genetic susceptibility in the host. Through genome sequencing analyses, and other studies over 240 distinct genetic loci were found, where approximately 30 of such loci are shared between ulcerative colitis and Crohn's disease [40–42]. The examination of the genes and genetic loci linked to IBD reveals a number of pathways that are crucial for conserving intestinal homeostasis [43]. The first gene linked to Crohn's disease was identified as nucleotide-binding oligomerization domain 2 (NOD2), around just over a third of patients commonly have mutated with Crohn's disease [44,45]. Furthermore, genome-wide association studies (GWAS) have been found a large number of single-nucleotide polymorphisms (SNPs) in the IL-23R gene, which show a significant association with both ulcerative colitis and Crohn's disease [46,47]. However, other studies have contradicted the pathophysiological link between IBD and gut microbial factors. It has been suggested that the gut microbiota can provoke abnormal host immune responses in individuals with IBD [16,48,49]. Recent studies on the epidemiology of IBD also indicate that environmental factors play a substantial role in the pathophysiology of the disease. Among these factors, dietary habits have been identified as significant influencers in the onset of IBD [50]. Additionally, smoking appears to exacerbate Crohn's disease while protecting against ulcerative colitis, making it a disease-specific modifier [51,52]. Other environmental factors, such as psychological stress, appendectomy, diet, and medication, can also have an impact on the development of IBD [53]. It is still difficult to be sure on the mechanisms by which environmental factors affect the progression of IBD disease, despite the fact that numerous epidemiological studies have already linked those factors to the IBD's evolution [53].

3.2. Microbiome, gut health and interrelationship to IBD

Both local and systemic immune systems, as well as non-immune

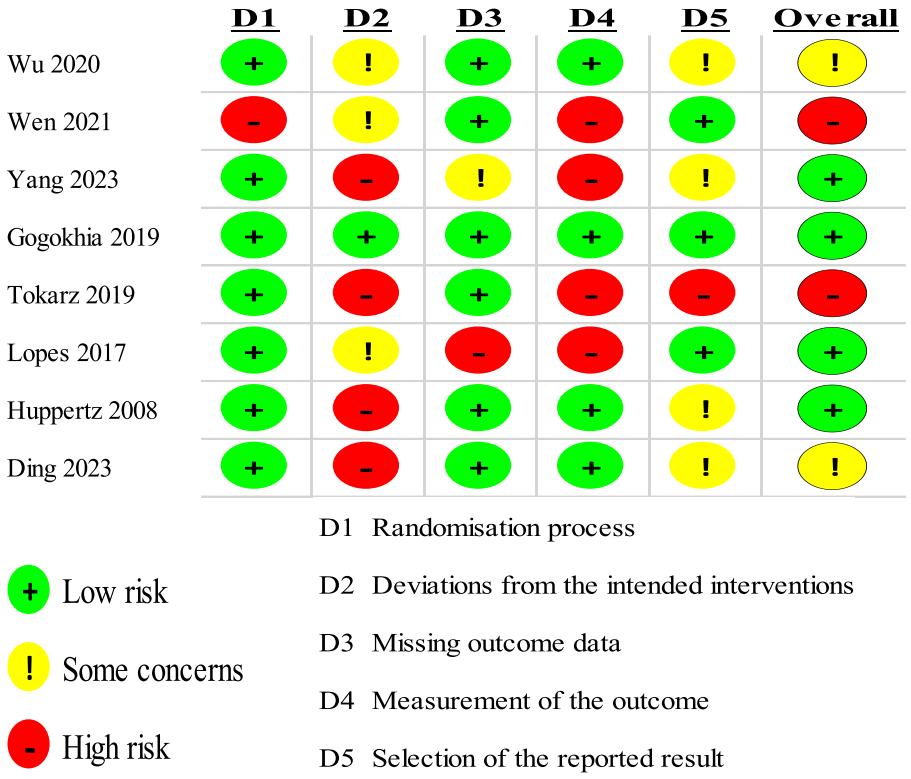


Fig. 3. Risk of bias assessment. According to the Cochrane risk-of-bias tool for randomized trials (RoB 2) Interventions, +: low risk of bias; -: high risk of bias; !: some concern risk of bias.

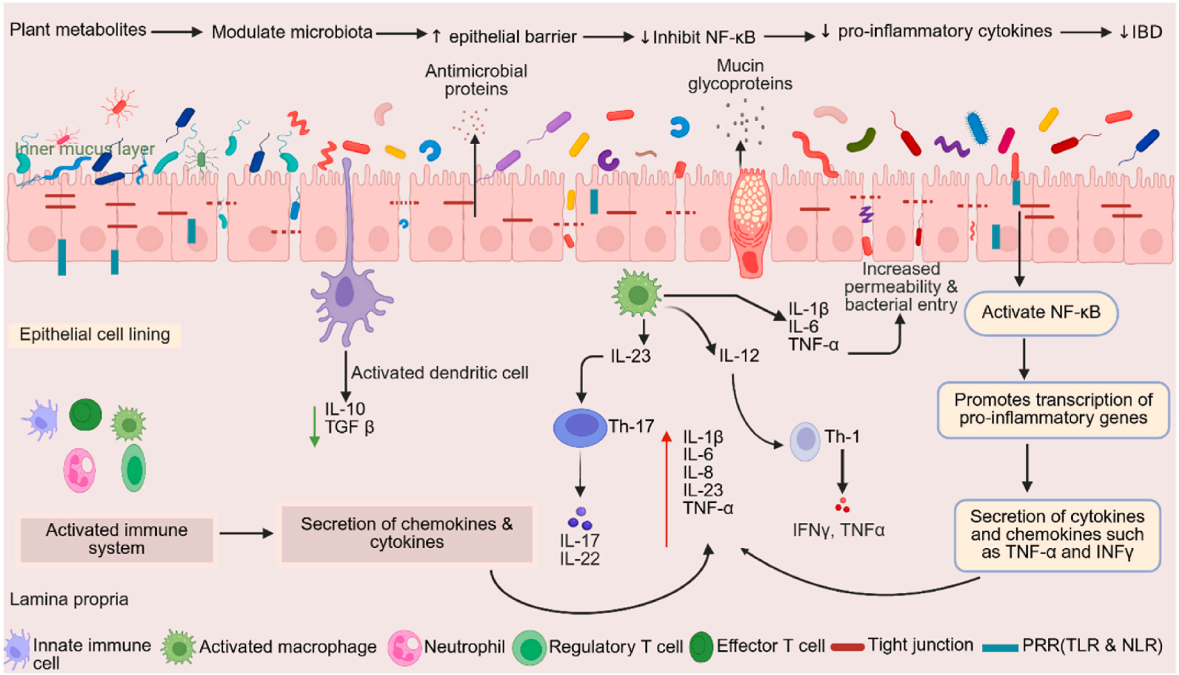


Fig. 4. Pathogenesis of inflammatory bowel disease (IBD) and the modulatory role of plant metabolites on gut-immune interactions. Pattern recognition receptors (PRRs) like Toll-like receptors (TLRs) and NOD-like receptors (NLRs) detect microorganism-associated molecular patterns (MAMPs) from both intra and extracellular bacteria. This recognition triggers the activation of nuclear factor-κB (NF-κB), which promotes the transcription of genes encoding pro-inflammatory cytokines and chemokines. NF-κB activation also plays a role in maintaining tissue homeostasis and mucosal tolerance, even in the absence of barrier damage. Activated lamina propria cells in the local tissue produce significant amounts of pro-inflammatory cytokines such as TNF, IL-1β, IFN-γ, and cytokines from the IL23/Th17 pathway. Plant-derived metabolites can beneficially modulate the gut microbiota, enhance epithelial barrier function, inhibit NF-κB signalling, and suppress pro-inflammatory cytokines. These effects collectively contribute to restoring gut immune balance and mitigating intestinal inflammation. This figure highlights the interplay between microbial dysbiosis, immune activation, and the protective role of plant metabolites in the pathogenesis of IBD [Created in https://BioRender.com].

components, rely on commensal microorganisms for their development and differentiation [49,54]. The outcome of an infection is influenced by both pathogenic and commensal microbes. Many microorganisms contain pathogen-associated molecular patterns (PAMPs), which can be identified by pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), C-type lectin receptors, and RIG-I-like receptors which plays a crucial role in identifying and responding to microbes [48,49,54]. Recognition of PRRs triggers the innate immune system, leading to the activation of NF-κB and inflammasomes that can promote tissue homeostasis and mucosal tolerance, even without barrier disruption, by stimulating the production of proinflammatory cytokines and chemokines, summarised in Fig. 4 [54,55]. Immunological dysregulation is characterised by an inability of immunological modulation to restrain the inflammatory reaction, alongside imbalanced intestinal microbes and significant infiltration of various cells into the lamina propria, including T and B lymphocytes, macrophages, dendritic cells (DCs), and neutrophils [56–58]. In the local tissue, activated lamina propria cells produce significant quantities of proinflammatory cytokines, including TNF-α, IL-1β, IFN-γ, and cytokines of the IL-23/Th17 pathway [56,57]. Among genetic contributors to IBD, NOD2 is one of the most well-established risk factors for Crohn's disease, with loss-of-function mutations impairing the host's ability to sense bacterial components, thereby contributing to microbial-induced immune dysregulation in IBD pathogenesis [59]. Recent evidence strengthens the connection between microbial-host interactions by highlighting that NOD2 not only functions in pathogen detection and phagocytosis but also plays a pivotal role in neutrophil-mediated inflammatory responses [60,61]. Specifically, NOD2 dysfunction is associated with impaired microbial containment and altered interactions with key commensals, such as *Faecalibacterium prausnitzii* and *Bacteroides fragilis*, highlighting its central role at the host-microbiota interface [62,63]. This axis underscores how gut microbiota can trigger aberrant immune responses through NOD2, contributing to sustained inflammation and tissue damage in Crohn's disease [60–62,64,65].

Plant based diet being one of the most crucial factors that greatly influences the composition of microorganisms, it is also associated with host immunity and the morpho-functional integrity of the intestinal barrier [66]. Variations in dietary patterns, particularly those rich in plant-derived nutrients, lead to significant alterations in microbial community profiles [67]. Consuming Mediterranean-style foods such as fruits, vegetables, whole grains, legumes, nuts, seeds promotes the growth of beneficial commensal bacteria, thereby enhancing host immune functions [68]. In order to identify the primary and coarse-modulating impacts of the MedDiet on the gut microbiome, it is feasible to state that there is a widespread and consistent trend toward the phylum *Firmicutes* and related taxonomic units changing from dominating structure to lower abundance while increasing the abundance of the *Bacteroidetes* phylum [69].

Extensive research has demonstrated the therapeutic efficacy of plant extracts and compounds against experimental models of inflammatory bowel disease. According to Lin et al. [70] study, an aqueous extract from *Bruguiera gymnorrhiza* (L.) Rhizophoraceae can modulate inflammatory cytokines TNF-α, TNF-γ, and IL-6 along with other indicators of oxidative stress and inflammation, also ability to decrease the levels of inducible nitric oxide synthase (iNOS). Another study by Guo et al. [71] found that ginger preparation alleviated ulcerative colitis in mice by reducing disease activity index scores, preventing colon shortening, lowering levels of IL-6 and iNOS, improving spleen index, and reducing the severity of mucosal injury. However, there are approximately 10,000 distinct phytochemicals, which are primarily divided into five groups: polyphenols, glycosinolates, carotenoids, alkaloids, and terpenes [72]. In vitro and animal models have demonstrated the involvement of these compounds in multiple biological processes: scavenging radicals, triggering anti-inflammatory reactions, regulating

gut microbiota homeostasis, activating intestinal T regulatory cells, maintaining mucosal barrier integrity, and controlling inflammatory pathways [73]. Polyphenols, also achieve their anti-inflammatory effects by blocking TLR4/NF-kB signalling pathways and suppressing the expression of molecules that promote inflammation [74]. The benefits of phytochemicals for health are also associated with the regulation of various microRNAs, which are involved in the control of the Th17 signalling pathway, T-cell differentiation, and the intestinal epithelial barrier. Additionally, they disrupt certain pathways related to inflammation signalling (NF-kB) and signal transducer and activator of transcription (STAT/IL-6) pathways [75]. Specifically, the bioactive elements of the plants, such as aloein, arctigenin, boswellic acid, curcumin, shagol, gymnemic acid, and cannabidiol, have been successfully utilized to treat ulcerative colitis [76–81]. Additionally, clinicians are now interested in using anthocyanins, which are polyphenols with purple, violet, or blue colors, to treat ulcerative colitis because studies have shown that plants like blueberries, bilberries, black raspberries, cranberries, and grapes can help in animal models of inflammatory bowel disease [82]. A meta-analysis of 7 placebo-controlled clinical trials involving 474 patients, conducted by Rahimi et al. [83], indicates that herbal remedies may help induce remission in IBD patients. According to Guo et al. [84], Red Ginseng enhanced the gut microbiota structure in rats with TNBS-induced colitis by promoting the colonization of *Lactobacillus* and *Bifidobacterium*, while inhibiting the growth of *E. coli*.

3.3. Virome and possible relation with IBD

3.3.1. Virome and human IBD

The gut virome exerts a substantial influence on immunity, inflammation, physiology, and disease. Our comprehension of the gut virome's role in IBD is relatively recent. The human gut virome consists of eukaryotic viruses, encompassing both DNA and RNA viruses, as well as bacteriophages (viruses that infect bacteria) [85], summarised in Fig. 5. The pathophysiology of ulcerative colitis and Crohn's disease has been associated with eukaryotic viruses that target DNA and RNA, which have the ability to transmit their genetic material directly to host cells [86]. The coexistence of viruses and bacteria in the gut has garnered increased attention, prompting some studies to concentrate on elucidating the roles of viruses in both pathogenic conditions and gut homeostasis [87]. The most extensively studied on eukaryotic viruses that may contribute to gut inflammation are Epstein-Barr virus (EBV) and cytomegalovirus (CMV). Both CMV and EBV, members of the *Herpesviridae* family, are typically asymptomatic and can remain latent throughout a person's healthy life [88]. There are evidence suggesting that eukaryotic viruses may serve as potential triggers of intestinal inflammation. To further extend, study conducted by Ding et al. [89] found three viruses—a polyomavirus, an anellovirus, and a novel CRESS-DNA virus, which are more prevalent in individuals with Crohn's disease in contrast to healthy ones. These viruses could eventually be used as diagnostic markers for the Crohn's disease. Another study by Huppertz et al. [90] suggests that rotavirus infection may exacerbate chronic IBDs, including Crohn's disease and ulcerative colitis. Adenovirus, rotavirus, and calicivirus were among the very few enteric viruses found in the feces of newly diagnosed patients with ulcerative colitis, according to research on 70 paediatric IBD patients employing high-throughput sequencing (VirCapSeq-Vert) for virome analysis [91]. Many families of viruses, including the *Anelloviridae*, *Adenoviridae*, *Astroviridae*, *Picornaviridae, Parvoviridae*, and *Picobirnaviridae*, begin to colonize the gut mucosa early in childhood, and as people mature, their diversity rises [24]. These viruses in the gut may either induce symptomatic manifestations or remain latent for extended periods in healthy individuals, and they could potentially exert beneficial effects [24].

3.3.2. Virome characteristics of IBD

Animal studies have demonstrated that specific eukaryotic viruses have the capacity to initiate inflammatory bowel disease in experimental models, highlighting their potential role in the pathogenesis of the disease [27]. For instance, intestinal infections caused by norovirus in Atg16L1-deficient mice result in intestinal disorders that, in a manner reliant on commensal bacteria, resemble Crohn's disease [92]. Similarly, chronic intestinal inflammation and disruption of the epithelial barrier were caused by norovirus infection in mice lacking IL-10 [93]. These findings imply that eukaryotic viruses may play a role in mediating pathogenic manifestations in genetically dependent hosts by potentially operating in a "hit-and-run" manner, making infections undetectable following viral clearance. In patients with Crohn's disease, the intestinal mucosa has shown an enrichment of RNAs from the *Hepeviridae* family, which typically cause hepatitis in mammals whereas patients with ulcerative colitis have exhibited transcripts from the *Hepadnaviridae* family, which includes the hepatitis B virus (HBV). These findings suggest that the etiopathogenesis of IBD may be linked to these eukaryotic viral families [24].

Further investigations are necessary to better understand the

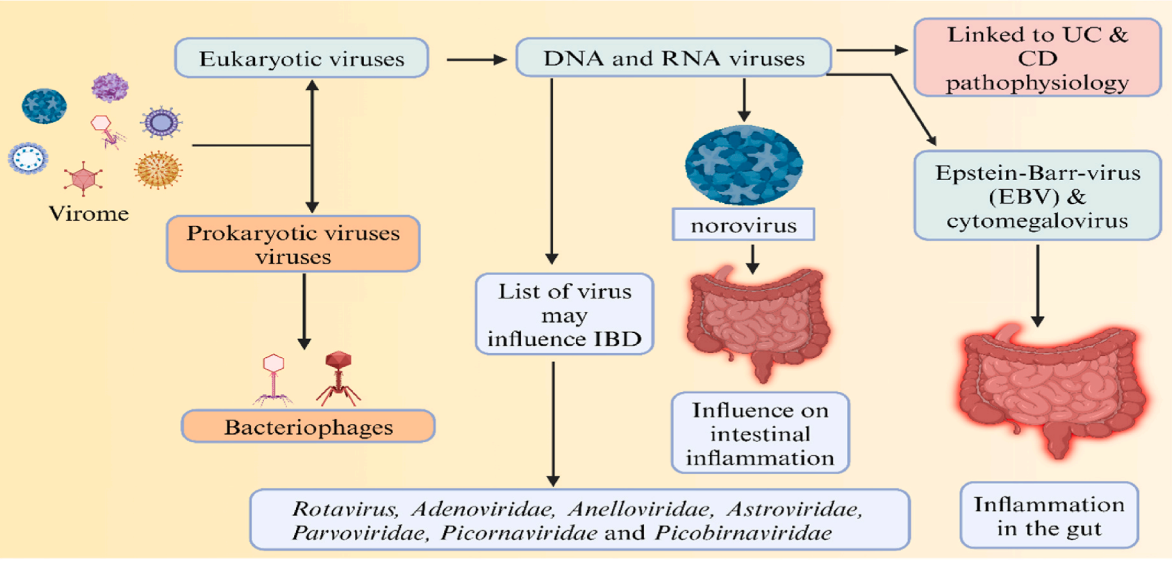


Fig. 5. Virome, including eukaryotic viruses, contributes to the pathogenesis of inflammatory bowel disease. DNA and RNA viruses like norovirus, EBV and CMV are well known to induce inflammation in intestines [Created in https://BioRender.com].

relationship between the virome and IBD, as well as to elucidate any potential mechanisms of action that may shed light on new avenues for studying IBD.

3.4. Bacteriophage's activity on IBD

Bacteriophages, commonly referred to as phages, plays a crucial part in gut microbiome regulation [94]. The main work of phages is to infect bacteria however, a number of studies have shown that eukaryotic cells and bacterial viruses can have interdependent relationships. Due to their ability to translocate into eukaryotic cells, it activates the immune system; phages can directly interact with the human body that aggravate the chronic colitis symptoms and enhancing the antibacterial response [95,96]. In recent years, phages have gained significant attention in the medical and microbiological fields because these viruses can be utilized to treat bacterial infections, especially given the growing concern over antibiotic resistance [97]. Several studies suggest that intestinal bacterial dysbiosis is a key factor contributing to IBD [98]. Researchers have observed higher relative abundance and growth rates of pathogenic bacteria, such as *Bacteroides fragilis*, in individuals with Crohn's disease and ulcerative colitis compared to healthy controls [99]. Another research also suggests that phages could be a viable therapeutic option for targeting pathogenic *Bacteroides fragilis* [100]. Additionally, *Ruminococcus torques* and *Ruminococcus gnavus* are found to be enriched in individuals with Crohn's disease and ulcerative colitis at the onset of the disease [101].

An estimate of the overall phage population in the human gut around 10^{15}, ten times higher than the number of gut bacteria (10^{14}). Besides their large population, gut phages can modify bacterial community structure by lysing and eliminating host bacteria, potentially influencing immune system modulation and contributing to inflammation reduction [98]. The dysbiosis of gut phages also contribute to the development or aggravation of gastrointestinal disease [102]. To date, a significant amount of research has been done using both clinical samples and experimental models to illustrate the connection between the start and progression of IBD and gut phage homeostasis [21,103,104]. Based on experimental findings, it has been postulated that gut phages could have been involved in the development of IBD through three pathways: (1) altering gut phage diversity, (2) regulating gut bacterial populations, and (3) modulating pro-inflammatory activity and local immune responses [98]. Some research also witnessed a synergistic effect of using plant extracts and bacteriophages together against bacteria. The combined treatment of 0.1 mg/ml neem extract with an isolated phage vB_EcoM_C2 at a titer of 10^{11} effectively controlled the growth of *E. coli* E1 [105]. Additionally, phages have demonstrated therapeutic effects against IBD and may also contribute negatively to its development. Further research is warranted to explore phage activity in treating IBD and to investigate the synergistic effects of plant extracts and phages against bacteria in the context of IBD.

3.5. Natural products and microbial communities

Gut microbiota (GM) is essential for maintaining the integrity of the intestinal barrier and performs crucial roles in host pathophysiological processes, including the development of the immune system, nutrient absorption, energy metabolism, and the maturation of the intestinal mucosal barrier [106]. Research suggests that a reduction in the diversity and abundance of harmful gut microbiota is linked to a higher incidence of colitis [107]. In the host gut lumen and mucosa, over 10^{14} commensal bacteria coexist that impacting the immune system and metabolic processes [108]. The homeostasis of the gut microbiome is essential to the maintenance of gut health. To maintain intestinal homeostasis, it is necessary to regulate the colonization of probiotic bacteria, prevent bacterial transmission into colon tissue, and regulate the colonization of pathogenic bacteria [108]. The gut microbes have a significant impact on the intestinal barrier. The symbiotic relationship of bacteria with the gut plays a crucial role in protecting the gut barrier by improving the mucus layer, regeneration of Tight junctions (TJs), and regulating the growth and apoptosis of the epithelial cells [109]. Some preclinical studies have reported that plant metabolites possess anti-inflammatory properties and are capable of modulating the gut microbiome [110]. The anti-inflammatory properties have been attributed primarily to plant metabolites belonging to the polyphenol, terpenoids, flavonoid, saponin, and tannin families [111].

Short-chain fatty acids (SCFAs) are key elements for gut health, and their production is largely related to the gut microbiome through the fermentation of dietary fibres, which has the potential to reshape gut ecology, modulate immune responses and antibiotic activity, and influence inflammatory signalling cascades during gut inflammation [112]. In recent times, there is increasing interest in the role of short-chain fatty acids in immune modulation, particularly through the signalling pathways mediated by G protein-coupled receptors (GPRs) and Toll-like receptors [113]. A study found that SCFAs exposure in pre-adipocytes triggered an innate immune response, suggesting that maintaining optimal SCFA levels is crucial for effective immune regulation in inflammatory diseases [114]. In the human colon, short-chain fatty acids are predominantly found in the following proportions: acetic acid (acetate) constitutes about 60 %, while propionic acid (propionate) and butyric acid (butyrate) each make up around 20 % [115]. *Firmicutes* species, such as *Lactobacillaceae*, *Ruminococcaceae*, and *Lachnospiraceae*, can break down complex polysaccharides and different sugars through hydrolysis, leading to the formation of butyrate and other short-chain fatty acids [116,117]. Microbial communities that produce butyrate are vital for a healthy gut, as they play a key role in blocking the entry and colonization of harmful pathogens [118]. Butyrate production by these bacteria is crucial for colonocytes to produce energy and boost epithelial oxygen consumption [119,120]. Patients with UC appear to have decreased SCFA production as well as inhibited butyrate uptake and oxidation [121]. As a result, their anti-inflammatory activity is diminished, which accelerates the course of the illness. SCFAs also help to lower the levels of proinflammatory cytokines by inhibiting the activity of NF-κB and histone deacetylases (HDACs) [122–124], and to an increasing the levels of anti-inflammatory cytokines through the activation of G-protein-coupled receptors (GPCRs) [125].

Plant compounds exhibit diverse effects on the microbiome; while some enhance beneficial bacteria and reduce harmful ones, others have the opposite effect, promoting harmful bacteria and diminishing beneficial ones (Fig. 6 and Table 1). Therefore, the activity of plant metabolites on the microbiome depends on the specific interactions between different types of metabolites. Caffeic acid, luteolin, isoorientin, resveratrol, ursolic acid, genistein, apigenin, betaine, and other plant metabolites have been shown to increase beneficial bacterial phyla and genera such as *Bacteroidetes, Firmicutes, Campylobacterota*, and *Akkermansia*, while decreasing bacterial phyla and genera that have negative impacts related to inflammatory bowel disease (IBD), such as *Proteobacteria*; additionally, some metabolites also reduce *Actinobacteria, Bacteroidetes, Firmicutes*, and others [126–132]. This context-specific modulation reveals the complexity of phytochemical–microbiome interactions and highlights the importance of identifying bioactive compounds with consistent anti-inflammatory profiles.

Once ingested, many plant compounds are bio-transformed by the gut microbiota into secondary metabolites with enhanced bioactivity and therapeutic potential [133]. Emerging evidence suggests that these metabolites play a pivotal role in modulating immune responses and maintaining intestinal homeostasis. Key phytochemicals including quercetin, curcumin, and resveratrol are metabolized into derivatives such as dihydroresveratrol, urolithins, and sulfated or methylated forms, which exhibit amplified anti-inflammatory properties [134–136]. These metabolites are capable of suppressing key pro-inflammatory mediators such as TNF-α, IL-6, and NF-κB in colonic tissues [137]. Additionally, microbiota-mediated transformations generate SCFAs and secondary bile acids (SBAs), which collectively upregulate P-glycoprotein (P-gp)

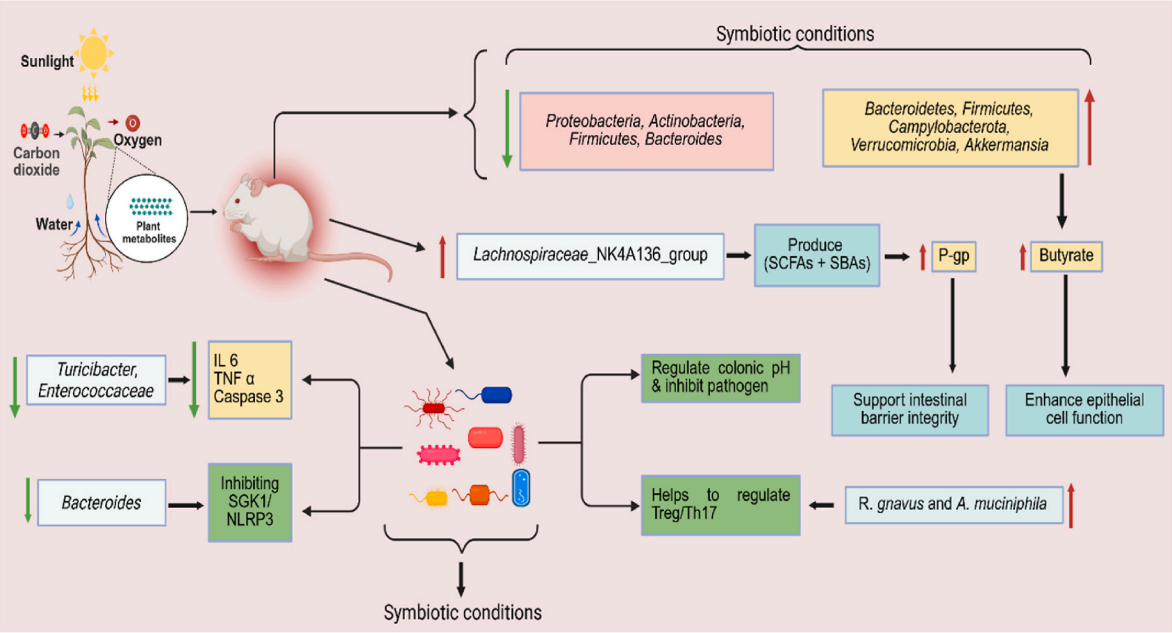


Fig. 6. Mechanism of action of plant-derived compounds on IBD and microbiome. Plant metabolites can have dual effects on the microbiome: some promote the growth of both beneficial and harmful bacteria, while others inhibit their growth. These metabolites play a crucial role in supporting the intestinal barrier by facilitating the conversion of certain bacterial metabolites into short-chain fatty acids (SCFAs) and secondary bile acids (SBAs). Through these mechanisms, plant metabolites assist microbiomes in reducing inflammatory cytokines such as IL-6, TNFα, and caspase-3. They also regulate the balance of Treg/Th17 cells, inhibit SGK1/NLRP3 pathways and regulate colonic pH. Controlled pH helps to suppress pathogenic substances linked to inflammatory bowel disease inducing factors [Created in https://BioRender.com].

expression and enhance butyric acid (i-butyric acid) production, further reinforcing the intestinal barrier [127,130,138].

The synergistic interaction between plant metabolites and the gut microbiota also modulates critical immune pathways, including suppression of the SGK1/NLRP3 axis, reduction of caspase-3 activity, and rebalancing of the Treg/Th17 cell ratio. Moreover, *Firmicutes* contribute to inhibiting intestinal inflammation by regulating colonic pH and suppressing pathogen growth [128,139–142]. As summarised in Table 1, these insights provide a framework for exploring plant metabolites and their potential interactions with the microbiome, highlighting emerging outcomes that signify a new era in IBD research.

4. Discussion

Intestinal microbes are one of the key factors driving the development of colitis by influencing the inflammatory processes within the gastrointestinal tract. According to a recent study, gut microbiomes have significantly dysregulated in experimental animal models and patients with IDB [158–161]. *Bacteroides and Firmicutes* are the two main phyla that constitute intestinal microorganisms [162]. As per clinical study, patients with ulcerative colitis had a lower *Firmicutes* to *Bacteroides* ratio (F/B), while *Proteobacteria* became much more prevalent in colitis-affected mice and were also a hallmark of gut dysbiosis [163,164]. From an immunological perspective, the dysregulation of Treg/Th17 cell differentiation stands as a pivotal factor influencing the onset, progression, and prognosis of IBD [165]. The pathogenic microorganisms and their bacterial byproducts act directly on TLRs and trigger DCs to release TGF-β and IL-6, which causes naïve $CD4^+$ T cells to mature into Th17 cells [166]. In addition to protecting the intestinal mucosa by eradicating pathogens, Th17 cells can intensify the inflammatory response within the gut by producing pathogenic cytokines such as IL-17F, IL-17A and IL-22 [167].

Conversely, Treg cells primarily contribute to immune tolerance maintenance through the secretion of IL-10, which prevents intestinal inflammation [168]. Several investigations have demonstrated that the composition of gut microbiota can influence Treg/Th17 differentiation [169]. Besides bacteria, a significant portion of the gut microbiota consists of viruses that infect both eukaryotic and prokaryotic cells, collectively forming the gut virome. The pathogenesis of IBD has been linked to eukaryotic virome dysbiosis because these viruses integrate into the genome of human and may affect the physiological condition of intestinal cells [170–173]. A comprehensive metagenomic analysis of a significant number of patients with ulcerative colitis revealed higher enrichment of the eukaryotic *Pneumoviridae* family in UC patients compared to controls, while the eukaryotic *Anelloviridae* family was more prevalent in controls than in UC patients [174]. In parallel, prokaryotic viruses such as bacteriophages also play a critical role in shaping gut ecology and potentially influencing IBD pathogenesis. It is hypothesized that these phages affect human health by influencing the structure of the bacterial microbiome [15]. However, the precise function of the phages in relation to intestinal homeostasis and illness is still unknown. It is important to note that the gut phageome in healthy adults is characterized by significant diversity and individual variability, with crAss-like and *Microviridae* phages being the most consistently present colonizers in a healthy state [175].

The predominate bacterial taxa, including *Bacteroides*, *Prevotella*, and *Faecalibacterium,* are correlated with these stable intestinal phage populations [15]. Plant metabolites have traditionally been used to treat various diseases, including inflammation [176]. Due to the anti-inflammatory [36] and microbiome modulation activity of plant metabolites summarised in Table 1, we can assume that plant metabolites have the capacity to influence the murine models of colitis that helps to enhance the presence of beneficial bacteria while reducing harmful ones.

Despite these promising findings, numerous challenges persist before plant compounds can be effectively utilized for modulating the gut microbiota in treating colitis. Primarily, investigations of plant metabolites activity on gut microbiota conducted only in preclinical models. There are significant anatomical differences between the gut compartments of mice/rats and humans, as well as variations in the composition

Table 1
| Effects of plant metabolites on microbiota against IBD and their possible outcomes.

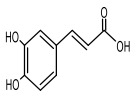
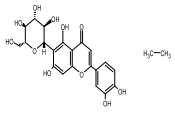
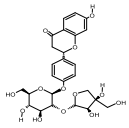
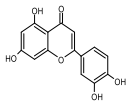
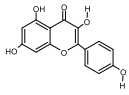
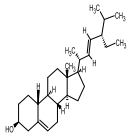
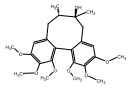
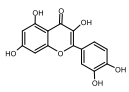
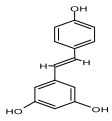
Plant metabolites/ extracts	Chemical structure	Major classes	Source	Effects on microbiota composition	Outcomes	References
Caffeic acid		–	coffee, oats, wheat, rice, argan oil, and olive oil	↓*Bacteroides*, ↓*Turicibacter*, ↑*Alistipes*, ↑*Dubosiella*, ↑*Akkermansia*	lowering *Bacteroides* reduces pro-inflammatory cytokines, *Akkermansia* increases anti-inflammatory ability and correlates with IL-10 mRNA expression, in colon tissue, *Dubosiella* was shown to be linked with the mRNA synthesis of HO-1, Gpx1, Gpx2, Nrf-2, and IL-10, indicating a potential function for the bacterium in promoting antioxidative and anti-inflammatory properties.	[126]
Isoorientin		Flavonoid	bamboo leaves	↑*Bacteroides* (*Lachnospiraceae*_NK4A136_group)	synthesis of serum bile acids (SBAs) and functional short-chain fatty acids (SCFAs) together increase the expression of P-glycoprotein (P-gp).	[128]
Liquiritin apioside		Flavonoid	*Glycyrrhiza aspera*	↓*Bacteroidetes*, ↑Firmicutes	corrected the unbalanced Treg/Th17 differentiation while stimulating the synthesis of SCFAs	[140]
Luteolin		Flavonoid	*Capsicum annuum* L., *Ghrysanthemum indicum* L., and *Perilla frutescem* (L.)	↑*Bacteroidetes* & ↓(*Firmicutes* and *Proteobacteria*)	functions of the microbiota were purine metabolism, ribosome function, pyrimidine metabolism, DNA repair and recombination proteins, and peptidases	[127]
Kaempferol		Flavonoid	green leafy vegetables, including spinach and kale, and herbs such as dill, chives, and tarragon	↑(*Prevotellaceae* & *Ruminococcaceae*), ↓*Proteobacteria*	controlling kaempferol's function	[143]
Stigmasterol		Phytosterol	*Ophiopogon japonicus, Mirabilis jalapa*	↑(*Ruminococcus*, *Prevotella*, *Helicobacter*, *Paraprevotella*, *Clostridium_IV*, *Odoribacter*, & *Clostridium_XlVa*); ↓(*Streptococcus*, *Escherichia*, *Enterococcus* & *Allobaculum*)	restores the balance of Treg/Th17 cells, increased the synthesis of gut microbiota-derived SCFAs	[144]
Schisandra chinensis extract	–	–	*Schisandra chinensis* (Turcz.) Baill.	↑*Bacteroidetes*, ↓*Actinobacteria*	produce conjugated linoleic acid, which has a preventive impact on UC, and they support the gut flora's balance	[138,145]
Schisandrin		Lignans	*Schisandra chinensis*	↑*Lactobacilli* spp, ↓*Bacteroides*	SGK1/NLRP3 signalling pathway's inhibition, converting primary to secondary bile acids, and altering the gut microbiota	[146]
Quercetin		Flavonoid	citrus fruits	↑(*Bacteroides*, *Bifidobacterium*, *Lactobacillus*, and *Clostridia*),↓ (*Fusobacterium* & *Enterococcus*)	improve gut protection	[139]
Resveratrol		Flavonoid	grapes, blueberries, raspberries, and peanuts	↑*Ruminococcus* (R. *gnavus* and *A. muciniphila*), ↓*B. acidifaciens*	increasing i-butyric acid production, Treg induction, and suppression of inflammatory Th1/ Th17 cells	[147]

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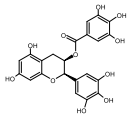
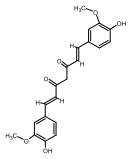
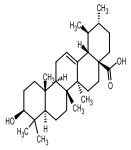
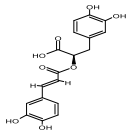
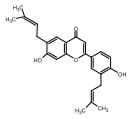
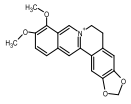
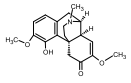
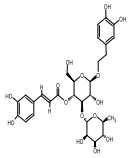
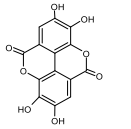
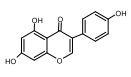
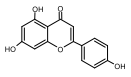
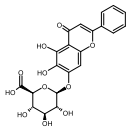
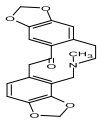
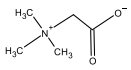
Table 1 (*continued*)

Plant metabolites/ extracts	Chemical structure	Major classes	Source	Effects on microbiota composition	Outcomes	References
Epigallocatechin-3-gallate		Flavonoid	green tea	↑(*Akkermansia*, *Faecalibaculum*, *Bifidobacterium*)	increased production of protective SCFAs	[148]
Ginger	–	–	*Zingiber officinale*	↓(*Proteobacteria*, *Firmicutes*, *Gemmatimonadetes*, *Lachnospiraceae*)	no specific data	[71]
Curcumin		Flavonoid	*Curcuma longa*	↑(*Coprococcus*, *Odoribacter*, *Akkermansia*), ↓(*Turicibacter*, *Enterococcaceae*)	helps to reduce inflammatory cytokine (IL-6, TNF-α) and caspase-3	[149]
Ursolic acid		Triterpenoid	*Lavandula angustifolia, Salvia officinalis, Ocimum basilicum, Origanum majorana, Melissa officinalis, & Satureja montana*	↑*Firmicutes* (*Lactobacillus*, *Bifidobacterium*, *& Ruminococcaceae_UCG-014)*, ↓(*Bacteroidetes*, *Actinobacteria*, *Verrucomicrobia & Proteobacteria*)	restored Treg/Th17 cell balance	[129]
Rosmarinic Acid		Polyphenol	Rosemary, *Prunella vulgaris*, and Oregano	↑*Bacteroidaceae*, ↓*Firmicutes*	helps to increase bioavailability and bioactivity	[150]
Licoflavone B		Flavonoid	*Lupinus albus, Glycyrrhiza glabra,* and *Glycyrrhiza inflata*	↑*Bacteroidetes*, ↓*Firmicutes*	inhibit inflammation and protect intestinal epithelium	[151]
Berberine		Alkaloid	*Cortex Phellode, Rhizoma Coptidis,* and Berberis	↑*Bacteroidetes*, ↓*Firmicutes*	microbiota responsible for controlling the Treg/ Th17 ratio	[152]
Sinomenine		Alkaloid	root of *Sinomenium acutum*	↑*Bacteroidetes*, ↓(*Firmicutes*, *Proteobacteria*)	not specified	[153]
***Echinacea purpurea* polysaccharides**	–	Polysaccharides	*Echinacea purpurea*	↑(*Firmicutes*, *Actinobacteria*), ↓(*Bacteroides*, *Proteobacteria*)	exert anti-UC effects	[154]
Acteoside		Glycoside	*Osmanthus fragrans* flowers	↑*(Odoribacter, A. muciniphila & B. thetaiotaomicron), ↓Desulfovibrio*	mediated the anticolitic effects of acteoside	[155]
Ellagic acid		Polyphenol	grapes, pomegranates, strawberries, persimmon, peaches, plums, almonds, walnuts, vegetables and wine	↑*Bacteroidetes*, ↓*Firmicutes*	colonic inflammation reduction was favourably correlated with gut microbiota	[156]
Genistein		Flavonoid	soybeans	↑*Firmicutes*, ↓(*Bacteroidota* & *Proteobacteria*)	promote the production of SCFAs	[130]
Apigenin		Flavonoid	celery	↑(*Verrucomicrobia*, *Bacteroidota*), ↓(*Proteobacteria* & *Firmicutes*)	inhibit inflammation and protect gut barrier	[131]

(*continued on next page*)

Table 1 (*continued*)

Plant metabolites/ extracts	Chemical structure	Major classes	Source	Effects on microbiota composition	Outcomes	References
Baicalin		Flavonoid	Huangqin	↑*Firmicutes*, ↓(*Proteobacteria* & *Actinobacteria*)	helps to produce SCFAs	[141]
Protopine		Alkaloid	*Macleaya cordata*	↑*(Firmicutes, Akkermansia)*, ↓*(Proteobacteria, Escherichia-Shigella, Enterococcus)*	*Firmicutes* control colonic pH and stop the development of pathogens to reduce intestinal inflammation	[142,157]
Betaine		–	beets, spinach, and whole grains	↑(*Bacteroidota*, *Campylobacterota*), ↓(*Firmicutes*, *Proteobacteria*)	helps to attenuate IBD	[132]

of their gut microbiota [177]. Therefore, translational gaps persist, highlighting the need for well-designed clinical trials to validate the therapeutic potential of these compounds in human populations.

Looking forward, the integration of virome research with phytochemical based therapeutic strategies represents a novel and promising direction for IBD treatment. Certain plant metabolites may exert dual activity-modulating both bacterial and viral components of the microbiota thereby offering a more comprehensive restoration of intestinal homeostasis [178,179]. Additionally, virome signatures, when combined with microbial and host biomarkers, may serve as innovative diagnostic tools for IBD subtypes [23,179]. Future research should aim to identify specific plant-derived compounds that can selectively influence virome structure and function, enabling the development of personalized, plant-based phage therapies and diagnostic platforms for IBD.

5. Conclusion

We cautiously embrace the potential impact of microbiome studies on our comprehension and management of IBD. There exists ample high-quality data supporting the hypothesis that altering the microbiome could play a crucial role in the onset and severity of IBD in certain patients. Researchers have extensively explored the microbiome to determine its potential role in IBD, though definitive conclusions have not yet been reached. Bacteria and virome (including eukaryotic and prokaryotic) are key components of the microbiome that exert significant effects on IBD. Plant metabolites also present an intriguing area of research for their anti-inflammatory properties and ability to modulate dysbiosis in the gut microbiota, potentially impacting IBD treatment. Further investigation is necessary to elucidate the pathophysiological mechanism of IBD, and their inter-connection with bacteria and viruses in response to using plant metabolites for the treatment of IBD.

CRediT authorship contribution statement

Md. Mizanur Rahaman: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Conceptualization. **Phurpa Wangchuk:** Writing – review & editing, Supervision, Conceptualization. **Subir Sarker:** Writing – review & editing, Supervision, Software, Resources, Methodology, Funding acquisition, Conceptualization.

Data availability

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

Funding

This research received no external funding.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Sarker is the recipient of an Australian Research Council Discovery Early Career Researcher Award (grant number DE200100367) funded by the Australian Government. The Australian Government had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.micpath.2025.107608.

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