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REVIEW

Polyphenols mitigating inflammatory mechanisms in inflammatory bowel disease (IBD): focus on the NF-ℵB and JAK/STAT pathways

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Abstract

The term "inflammatory bowel disease" (IBD) refers to a group of chronic inflammatory gastrointestinal disorders, which include ulcerative colitis and Crohn's disease. The necessity for alternative therapeutic approaches is underscored by the fact that although present medicines are successful, they frequently result in considerable adverse effects. Naturally occurring substances included in fruits and vegetables called polyphenols have been shown to have the capacity to control important inflammatory pathways including NF-κB and JAK/STAT, which are essential for the pathophysiology of IBD. The processes by which polyphenols, such as curcumin, EGCG, resveratrol, and quercetin, reduce inflammation are examined in this article. Polyphenols may have therapeutic advantages by blocking the synthesis of cytokines and the activation of immune cells by targeting these pathways. Preclinical study indicates a reduction in intestinal inflammation, which is encouraging. However, more clinical research is needed to determine the clinical relevance of polyphenols in the therapy of IBD, especially with regard to their long-term safety and bioavailability.

Keywords Inflammatory bowel disease (IBD) · Polyphenols · NF-κB · JAK/STAT · Inflammation

Introduction

Inflammatory bowel diseases (IBD), encompassing Crohn's disease and ulcerative colitis, are chronic, relapsing conditions marked by persistent inflammation of the gastrointestinal tract (Tili and Michaille 2016; Tran et al. 2012). Patients with these conditions often experience devastating symptoms such as chronic diarrhoea, rectal bleeding, abdominal pain, and weight loss. The precise aetiology of inflammatory bowel diseases remains elusive, but it is thought to involve a complex interplay of genetic susceptibility, environmental factors, disrupted gut microbiome, and an aberrant immune response (Saez et al. 2023).

Current treatments for inflammatory bowel diseases often focus on suppressing the overactive immune response and reducing inflammation. However, these therapies can have significant side effects, and many patients continue to experience persistent or recurring symptoms (Cai et al. 2021). Existing therapies, such as corticosteroids and immunosuppressants, often result in long-term side effects, including increased infection risk and reduced response over time (Mustafa 2023; Williams 2018). This therapeutic gap highlights the need for safer, long-term alternatives. As such, there is a growing interest in exploring alternative and complementary approaches, such as dietary interventions, to manage inflammatory bowel diseases (Yahfoufi et al. 2018a).

Polyphenols are a diverse class of plant-derived compounds with well-documented anti-inflammatory properties (Pereira and Cotas 2023). Several preclinical studies demonstrating the anti-inflammatory effects of polyphenols, such as curcumin (He et al. 2015), resveratrol (Meng et al. 2021), and epigallocatechin gallate (EGCG) (Mokra et al. 2023), have shown their ability to regulate key inflammatory

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pathways in IBD. These polyphenols modulate the NF-κB and JAK/STAT pathways, known to play critical roles in IBD pathogenesis (Ferreira et al. 2024; Yu et al. 2022). Inhibition of the NF-κB pathway by polyphenols can lead to decreased production of proinflammatory cytokines, chemokines, and adhesion molecules, thereby dampening the inflammatory response (Guo et al. 2024a; Mamun et al. 2024). Similarly, polyphenols have been observed to suppress the JAK/STAT pathway (Bose et al. 2020), which is involved in the regulation of immune cell function and the production of inflammatory mediators (Yahfoufi et al. 2018a; Yin et al. 2021). Emerging clinical trials also suggest that polyphenols could alleviate inflammation and improve symptom management in IBD patients (Ban et al. 2022; Jamieson et al. 2023). By targeting these pivotal inflammatory pathways, polyphenols may offer a promising approach to mitigate the chronic inflammation associated with inflammatory bowel diseases (Shapiro et al. 2007).

Further research is needed to fully elucidate the mechanisms by which polyphenols exert their anti-inflammatory effects and to evaluate their clinical efficacy in the management of inflammatory bowel diseases. Nonetheless, the current evidence suggests that the incorporation of polyphenol-rich foods or supplementation may serve as a valuable adjunct to conventional therapies, potentially improving patient outcomes and quality of life (Aloo et al. 2023).

The epidemiology of IBD

Traditionally, it was considered that inflammatory bowel disease (IBD) primarily affected Western countries. According to a comprehensive 2012 study, Europe has the highest yearly incidence rates of ulcerative colitis (UC) and Crohn's disease (CD), with 24.3 and 12.7 cases per 100,000 person-years, respectively (Mokhtar et al. 2019). In comparison, Asia and the Middle East had the lowest rates of UC and CD, with 6.3 and 5.0 cases per 100,000 person-years, respectively (Mokhtar et al. 2019). While the incidence of IBD in Western countries has remained constant or witnessed small rises, there has been a substantial rise in Asian countries (Chen et al. 2023).

IBD has generally been considered uncommon in Malaysia, with minimal information on incidence and sociodemographic features. Malaysia's annual IBD incidence is 0.94 per 100,000 person-years (Mokhtar et al. 2019), with a crude incidence of 0.68 per 100,000 person-years (Hilmi et al. 2015). Over the last two decades, the incidence has progressively climbed (from 0.07 to 0.69 per 100,000 person-years), with the Indian population seeing the highest rates (1.91 per 100,000 person-years) (Aniwan et al. 2022). A recent study in Johor, Southern Peninsular Malaysia, showed similar findings, with a crude incidence of 0.68 per 100,000 person-years (UC: 0.27, CD: 0.36) (Cheong et al. 2018). This epidemic trend is primarily due to urbanisation and the adoption of Western food patterns. Furthermore, increased consumption of restaurant meals, food additives, and preservatives has been recognised as a risk factor for colorectal cancer, a long-term outcome of IBD in Malaysians (Burisch et al. 2013; Molodecky et al. 2012; Ye et al. 2015).

The particular pathophysiology of IBD is unknown, although it is assumed to be caused by a complex interaction of environmental, genetic, immunological, and microbiological factors (Kim & Cheon 2017). IBD symptoms include gut epithelium breakdown, loss of integrity, invasion of the lamina propria by inflammatory cells (e.g. B cells, T cells (Gomez-Bris et al. 2023), macrophages(Han et al. 2021), neutrophils (Fournier & Parkos 2012)), and increased production of pro-inflammatory cytokines including TNF-α, IL-1β, IL-6, (Alhendi & Naser 2023) and IFN-γ (Saez et al. 2023; Vebr et al. 2023). Further, modifications in the intestinal microbiota—such as higher levels of *Mycobacterium avium* subsp. paratuberculosis, adherent-invasive *Escherichia coli*, and *Clostridium difficile*, along with decreased numbers of anti-inflammatory bacteria—are frequently reported in IBD patients (Nishida et al. 2017; Santana et al. 2022; Wang et al. 2024). Interrupted signalling pathways also play an important role in the inflammatory cascade, contributing to the development of IBD (Jurjus et al. 2016; Khoramjoo et al. 2022; Pedersen et al. 2014).

Current treatment approaches and limitations

The standard treatment for IBD consists of drugs targeted at decreasing inflammation or sustaining remission (Cai et al. 2021). Corticosteroids, immunosuppressants, antibiotics, aminosalicylates, and biological agents X are some examples (Zenlea and Peppercorn 2014). Although many patients benefit from these treatments, a considerable proportion do not respond initially or show a decrease in therapeutic impact over time, and standard treatments are frequently associated with significant negative effects (Baryakova et al. 2023; Puccetti et al. 2024). Long-term corticosteroid treatment raises the likelihood of problems like osteoporosis (Puccetti et al. 2024; Van Staa et al. 2000). Many people stop taking immunosuppressants and aminosalicylates because they cause severe side effects such as increased susceptibility to infections and gastrointestinal pain (Cai et al. 2021; Park and Cheon 2022).

Corticosteroids, immunosuppressants, and biologic medicines are common IBD treatments that aim to reduce inflammation and keep patients in remission. Corticosteroids such as prednisone rapidly reduce inflammation but carry long-term side effects, including increased infections risk

and osteoporosis (Yasir et al. 2023). Polyphenols, by contrast, inhibit pathways like NF-κB with fewer side effects. Unlike corticosteroids, polyphenols target these inflammatory pathways with fewer side effects. Biologic therapy, such as anti-tumour necrosis factor (TNF) medicines, are extremely effective and have few adverse effects, but their use is limited due to their high cost (Engel-Nitz et al. 2015; Marsal et al. 2022). Furthermore, because IBD is a chronic ailment, medication regimens frequently need to be changed throughout a patient's life. The limits of current medicines highlight the need for novel ways to controlling IBD.

Immunosuppressants and biologic medicines, such as anti-TNF-α medications (e.g. infliximab), are effective but costly, with potential side effects including increased infection risk and gastrointestinal discomfort (Li et al. 2017; Shivaji et al. 2019). Polyphenols are an inexpensive, natural alternative that can supplement or replace these treatments with fewer side effects.

Inflammatory mediators: prostaglandins, leukotrienes and cytokines

Inflammatory mediators such as prostaglandins, leukotrienes, and cytokines play a central role in driving the inflammatory process in IBD. These mediators maintain the immunological response, resulting in tissue damage and inflammation in the stomach. Prostaglandins, derived from arachidonic acid via the cyclooxygenase (COX) pathway, contribute to inflammation by increasing vascular permeability and attracting immune cells to inflamed sites (Singh Bahia et al. 2014; Wang et al. 2021). Polyphenols like curcumin and resveratrol have been shown to inhibit COX-2 activity (Yarla et al. 2016), reducing the production of pro-inflammatory progstaglandins such as PGE2, which is commonly elevated in IBD patients (Magrone et al. 2019a).

Leukotrienes, synthesised from arachidonic acid through the 5-lipoxygenase (5-LOX) pathway, are also key players in inflammation, particularly by promoting neutrophil recruitment (Monteiro et al. 2014; Wang et al. 2021). Studies indicate that polyphenols, such as quercetin and EGCG, inhibit 5-LOX activity (Yahfoufi et al. 2018b), thus reducing leukotriene-mediated inflammation and contributing to a reduction in intestinal inflammation.

Additionally, polyphenols modulate the balance between pro-inflammatory cytokines (such as TNF- α, IL-1β and IL-6) and anti-inflammatory cytokines like IL-10. The downregulation of TNF- α, a critical mediator in IBD pathogenesis, is a major therapeutic target of both conventional drugs and polyphenols. Polyphenols' ability to suppress these cytokines while promoting the anti-inflammatory effects of IL-10 suggests their potential as effective modulators of the immune response in IBD.

Experimental and clinical investigation

Several preclinical investigations have shown that polyphenols work in animal models of IBD. Curcumin reduces inflammation in mouse models of colitis by blocking NF-κB activation and downregulating pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (Ali et al. 2012; Zhu et al. 2014).

Polyphenols' potential for treating human IBD has been investigated in clinical trials. For example, a clinical trial of curcumin as an adjuvant to standard therapy in ulcerative colitis patients found that it reduced disease activity and improved remission rates (Ali et al. 2012; He et al. 2015). EGCG, contained in green tea, has also been studied in therapeutic settings, with results indicating that it can lower inflammation indicators in Crohn's disease patients (Brückner et al. 2012; Mokra et al. 2023). However, larger, more extensive clinical trials are required to validate these findings and address issues such as bioavailability and dose.

Polyphenols and TLR/NLR signaling in IBD

Polyphenols, typically abundant in fruits and vegetables, have been demonstrated to modulate TLR and NLR signalling pathways, potentially providing anti-inflammatory benefits in IBD (Al-Khayri et al. 2022; Ferreira et al. 2024; Singh et al. 2020). Curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG) block TLR-mediated NF-κB activation and reduce inflammatory cytokine production (Cione et al. 2019; Liu et al. 2023; Magrone et al. 2019b). Curcumin, for example, has been demonstrated to impede TLR4 dimerisation, therefore limiting downstream signalling and cytokine generation (Panaro et al. 2020; Zhu et al. 2014). Quercitin, a flavonoid found in many fruits and vegetables, has also shown efficacy inhibiting TLR-mediated NF-κB and reducing intestinal inflammation in preclinical models (Zhang et al. 2023). Similarly, anthocyanins, found in berries, have been noted to regulate both TLR and NLR pathways, contributing to the reduction of intestinal inflammation and protection of the gut lining (Schneider et al. 2015).

Resveratrol has been widely researched for its anti-inflammatory properties in IBD (Gu et al. 2024). It has been shown to lower oxidative stress and inhibit inflammatory cytokines including TNF-α and IL-6 through the regulation of NF-κB and STAT3 pathways (Yaqin et al. 2024). EGCG, a significant polyphenol in green tea, has also been researched for its ability to reduce colonic inflammation by inhibiting STAT3 activation and lowering

the levels of pro-inflammatory mediators (Fan et al. 2017a, b; Mokra et al. 2023). The growing body of research on polyphenols highlights their ability to intervene at multiple points in immune signalling cascades, offering broad anti-inflammatory effects that are promising for IBD treatment enhancing the NF-κB and JAK/STAT. These polyphenols play a crucial role in modulating the chronic inflammation that characterises IBD. This review explores the molecular mechanisms through which polyphenols exert anti-inflammatory effects and evaluate their therapeutic potential in IBD.

Polyphenols have shown potential in improving clinical outcomes in IBD patients via modulating the NF-κB and JAK/STAT pathways. These pathways are important regulators of the inflammatory response, causing the generation of pro-inflammatory cytokines that contribute to the chronic inflammation found in IBD patients. By targeting these pathways, polyphenols such as curcumin, resveratrol, and EGCG can suppress the activation of immune cells, reduce cytokine production, and promote tissue repair. Clinically, this could lead to decreased disease activity, fewer flare-ups, and improved mucosal repair, thereby enhancing the quality of life for IBD patients. Furthermore, polyphenols' natural anti-inflammatory properties may make them a safer alternative to traditional medicines, which are frequently associated with negative side effects such as immunosuppression and infection risk. With ongoing research, polyphenols could become a valuable adjunct to standard IBD therapies, offering both enhanced efficacy and reduced side effects, leading to better long-term disease management.

The NF-κB pathway in IBD

NF-κB is a pivotal transcription factor that regulates the expression of pro-inflammatory genes, making it a crucial target for therapeutic interventions in IBD. The activation of NF-κB is triggered by various stimuli, including TLRs, cytokines, and bacterial products (Yu et al. 2020). Upon activation, NF-κB translocates to the nucleus, where it induces the transcription of genes encoding cytokines such as TNF-α, IL-1β, and IL-6, which drive the inflammatory response in IBD (Guo et al. 2024b).

By inhibiting NF-κB, polyphenols reduce the production of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6 while increasing levels of IL-10, an anti-inflammatory cytokine (Shakoor et al. 2021). Polyphenols such as curcumin, resveratrol, and luteolin have been shown to reduce NF-κB activity. Curcumin inhibits the IKK complex, reducing NF-κB translocation and pro-inflammatory cytokine production in colitis models. Resveratrol inhbitis NF-κB activation by reducing IκB kinase activity, which results in lower cytokine production and decreased inflammation in colitis animal models (Meng et al. 2021; Guo et al. 2024a; Mamun et al. 2024). This mechanism shows potential for future clinical applications. Berries include anthocyanins, which suppress NF-κB signalling and reduce intestinal inflammation (Ma et al. 2021). NF-κB modulation has important clinical importance for IBD patients, with treatments targeting this pathway potentially leading to reduced disease severity and better outcomes. However, clinical trials are required to assess the efficacy of polyphenol-based treatments in human IBD.

JAK/STAT pathway in IBD

The JAK/STAT signalling pathway is important in IBD because it mediates the effects of pro-inflammatory cytokines. Cytokines including TNF-α, IL-6, and IFN-γ stimulate the JAK/STAT pathway, resulting in the transcription of genes related to immune control and inflammation (Hu et al. 2021). Dysregulated activation of this system is linked to the aetiology of IBD, and JAK/STAT signalling inhibitors have emerged as promising therapeutics (Moon et al. 2021).

Polyphenols have demonstrated promise in altering JAK/STAT signalling (Moon et al. 2021). Curcumin, for example, suppresses STAT3 phosphorylation, lowering the production of inflammatory cytokines in mouse colitis models (He et al. 2015). EGCG, the major polyphenol in green tea, has also been demonstrated to inhibit STAT3 activation, resulting in less colonic inflammation in IBD models (Fan et al. 2017a, b).

Clinically, the ability to regulate the JAK/STAT pathway has implications for reducing inflammation and enhancing mucosal healing in IBD patients (Cordes et al. 2020). The ongoing development of polyphenol formulations with enhanced bioavailability could pave the way for their integration into standard IBD treatment regimens.

Conclusion

Polyphenols are a promising class of natural chemicals with great potential in the treatment of IBD. Polyphenols can control inflammation by targeting important signalling pathways such as NF-κB and JAK/STAT, providing a supplementary approach to conventional therapies. While preclinical studies show promise, clinical rials are necessary to address bioavailability challenges and validate polyphenols safety and long-term efficacy. Future research should focus on optimising polyphenol compositions to increase therapeutic potential and incorporate them into regular IBD treatment regimens.

Clinical trials are critical for confirming the benefits seen in preclinical models. These studies should seek to define optimal dosages, assess long-term safety, and investigate the possibility for polyphenols to be included into traditional IBD therapy regimens. Polyphenols may emerge as a beneficial adjuvant therapy in the treatment of IBD by addressing these issues, increasing patient results and quality of life.

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Data availability This study is a review article, and as such, no original data were generated or analyzed during the study. All data discussed are available in the cited references.

Declarations

Conflict of interest All authors declare that they have no conflicts of interest.

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