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Review paper

Anti-inflammatory natural products modulate interleukins and their related signaling markers in inflammatory bowel disease: A systematic review

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ABSTRACT

This review aims to identify in vivo studies investigating the potential of plant substances and their natural molecules in managing inflammatory bowel disease (IBD). Specifically, the objective is to examine the impact of these substances on interleukins and other key inflammatory signaling markers. Relevant articles published up to December 2022 were identified through a search of the PubMed, Scopus, Web of Science, and Embase databases. The search used keywords including "inflammatory bowel disease", "medicinal plants", "natural molecules", "anti-inflammatory", and "ulcerative colitis", and identified 1,878 potentially relevant articles, of which 89 were included in this review after completion of the selection process. This study provides preclinical data on natural products (NPs) that can potentially treat IBD, including ulcerative colitis. The main actions of these NPs relate to their effects on nuclear factor kappa B (NF-κB), the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathway, the regulation of T helper 17/regulatory T cells balance, and oxidative stress. The ability of these NPs to inhibit intestinal inflammation appears to be dependent on lowering levels of the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-17, via the Jun N-terminal kinase (JNK)1, NF-κβ-p65, and STAT3 pathways. In addition, NPs were shown to reduce oxidative stress and the severity of ulcerative colitis, as well as increase the activity of antioxidant enzymes. These actions suggest that NPs represent a promising treatment for IBD, and potentially have greater efficacy and safety than current treatments.

1. Introduction

Inflammatory bowel disease (IBD) is a persistent chronic gastrointestinal (GI) tract disorder, with its two main kinds being ulcerative colitis (UC) and Crohn's disease (CD), which are characterized by recurrent episodes of remission interspersed with chronic intestinal inflammation [1]. The progression of CD can affect any portion of the GI system, resulting in edema, ulceration, bleeding, and fluid and electrolyte losses. UC is restricted to the colon, starting in the rectum and extending to the proximal segments of the colon [2]. IBD-related chronic GI inflammation has

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crippling and occasionally deadly consequences, such as toxic megacolon, intestinal obstruction, bowel rupture, and malignancy. The exact causes of IBD are currently unknown; however, genetic differences, an unbalanced immune response to environmental changes, and an altered gut flora, are believed to play significant roles in its development [3]. Amplification and uncontrollable immune responses could result from luminal antigens moving into the intestinal wall due to genetic and environmental variables altering the epithelial barrier function [4]. The synthesis and release of numerous pro-inflammatory mediators, such as reactive oxygen and nitrogen metabolites, eicosanoids, chemokines, and cytokines, are consequently increased. These mediators actively contribute to the detrimental cascade that starts and feeds the inflammatory response in the gut [5]. The number of cases of IBD has increased globally because of greater industrialization and urbanization, and diagnostic advances [6]. A thorough understanding of its etiology is required to design a suitable treatment strategy and address the restrictions and shortfalls of the current therapy models.

The global prevalence of IBD is increasing rapidly. In Western countries, the estimated prevalence is between 0.3% and 0.5% of the population and is continuing to increase, with the greatest burden being in North America, Oceania, and Europe. The prevalence is also rising in newly industrialized nations in Asia, Africa, and South America [3]. IBD has emerged in the 21st century as a serious illness. In East Asian nations, the frequency of UC ranged from 0.95 to 12.2, whereas the incidence of CD reached 2.42. A distinct CD phenotype with a high prevalence of perianal fistula and a male predominance was also discovered in Asia. A study on the IBD epidemic in Asia predicted that by 2035 the estimated IBD prevalence in India would increase fourfold, while in West Asia it would increase by 2.3–2.5 times, and in East and Southeast Asia by 1.6–1.7 times [6].

2. Signaling pathways in IBD

2.1. Nuclear factor kappa B signaling pathway

Nuclear factor kappa B (NF-κB), a transcription factor, controls a wide range of biological activities and is a crucial regulator of inflammation [7]. Patients with IBD frequently have dysregulated NF-κB signaling, which causes abnormal cytokine and chemokine production in the gut. A series of NF-κB inhibitors (IκBα) maintain the NF-κB complex, RelA (p65)/p50 heterodimers in the cytoplasm in an inactive state [8,9]. When molecules like tumor necrosis factor-α (TNF-α) attach to TNF receptors, NF-κB is activated. Once the TNF receptors are triggered, a complex signal transduction cascade starts, which activates a large I Kappa B (IκB) kinase complex (IKK) made up of the regulatory subunit IκB kinase γ (IKKγ), the catalytic subunits IκB kinase α (IKKα), and IκB kinase β (IKKβ) [8]. The IKK complex phosphorylates IκBα upon upstream kinase activity, causing its disintegration and the subsequent release of the RelA/p50 heterodimer. RelA/p50 heterodimers that have recently been released go quickly to the nucleus to stimulate the transcription of a variety of inflammatory mediators, including cyclooxygenase (COX)-2, TNF-α, interleukin (IL)-1β, and IL-6 [10].

2.2. The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway

JAK/STAT pathway is crucial in cellular processes like cell division, cell death, and immune regulation, and is involved in numerous diseases. Its hyperactivation is linked to inflammatory and autoimmune diseases like rheumatoid arthritis, IBD, systemic lupus erythematosus, and psoriasis [11]. Mucosal immune and non-immune cells in the inflamed gut of IBD patients spontaneously release pro-inflammatory cytokines such as TNF-α, interferon-gamma (IFN-γ), IL-1β, IL-6, IL-8, and IL-12, which play a central pathologic role in IBD, although the mechanism responsible for this remains unknown [12]. These extracellular cytokines associated with IBD regulate inflammatory responses by activating the JAK-STAT pathway. The phosphorylation of JAK and tyrosine residues occurs due to the binding of cytokines to their respective receptors, causing the receptors to conformationally shift and alter the position of the associated JAK [13,14]. Tyrosine residues that have been phosphorylated serve as STATs' binding sites on cytokine receptors, and the recruitment of STAT to the receptor causes JAK to phosphorylate STAT. At some point, phosphorylated STATs separate from the docking sites on their receptors and form homo or heterodimers. They translocate from the cytoplasm to the nucleus to control gene transcription receptive to cytokines. The JAK-STAT pathway is an important intracellular downstream signaling route employed by several inflammatory cytokines that are elevated in IBD [15].

2.3. T helper type 17 (Th17)/regulatory T-cells imbalance

A subset of effector T cells known as Th17 are found throughout the mucosa, particularly in the intestinal mucosa. These cells mainly defend the host against microbial invasion by secreting inflammatory cytokines, such as IL-17A, IL-21, and IL-22, to control immunological responses [16]. Conversely, regulatory T-cells (Tregs) are a subset of T cells with immunosuppressive qualities that can control effector T cells by cell-cell contact or through the release of anti-inflammatory cytokines to maintain autoimmune tolerance and avoid damage inflicted by an excessive immune response [17]. From a naive cluster of differentiation 4 ($CD4^+$) T cells, Th17 and Treg cells are produced. Tregs immunologically monitor Th17 cells and suppress their excessive immune response, while Th17 cells produce their cytokines to sustain the immune response required to protect the host from infection [18]. As a result, there is an immunological equilibrium between Th17 and Treg cells. Several pathogens enter the intestinal epithelial barrier when IBD is prevalent, stimulating antigen-presenting cells (such as dendritic cells and macrophages) and causing them to release inflammatory cytokines such as IL-1β, IL-6, and IL-23 [19]. Naive $CD4^+$ T cells that are produced as a result are more likely to produce Th17 cells. The continual build-up of Th17 cells causes an excessive production of inflammatory cytokines, which causes a strong inflammatory response that far exceeds the immunological tolerance of Tregs and leads to the onset of IBD [20,21].

3. The etiology of IBD

The scientific evidence suggests that environmental exposures, such as air and water pollution, and food additives, have a significant impact on IBD and other chronic inflammatory illnesses [22], with risk factors also including other autoimmune illnesses, smoking, sleep disorders, infections, medications, and stress. In addition, epidemiological studies suggest genetic factors play a role in the etiology of IBD. For example, blood relationships of UC and CD individuals have been shown to have an 8 to 10 fold higher chance of developing IBD [3]. The spread and worsening of IBD have also been closely linked to inflammatory reactions and oxidative stress, and are defined as an imbalance between prooxidants and antioxidants. A change towards prooxidants is caused by invading mucosal tissue with activated phagocytic immune cells that produce reactive oxygen and nitrogen species (ROS and RNS,

respectively) [20]. This disrupts cellular homeostasis by injuring essential macromolecules, adds to cell damage, increases mucosal barrier permeability, and intensifies already present inflammation. The inflammation-mediated upregulation of different lipoxygenases, myeloperoxidase (MPO), and inducible isoforms of nitric oxide (NO) synthase (NOS2), COX-2, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase produce RNS, which are typically highly reactive and unstable molecules [21].

4. Existing IBD treatments

The mainstays of current clinical treatment for IBD are surgery and medications, although their efficacy cannot be guaranteed and their use is constrained by their side effects [23]. Anti-TNF-α agent therapy, for instance, raises the risk of opportunistic infection and malignant tumors [24]. Surgery is restricted by the patient's age and physical conditions, but it carries risks such as pelvic infection, severe hemorrhage, and intestinal perforation [24]. Therefore, it is crucial to create new IBD treatment strategies. Several research projects have examined the potential of natural products (NPs) and their compounds as possible treatments to prevent and treat IBD due to a range of characteristics, including anti-inflammatory properties that have been identified in NPs in studies related to other illnesses [12]. This review examines the current state of research in the use of NPs for the prevention and treatment of IBD.

5. Materials and methods

5.1. Methods

To perform this systematic review, the following steps were followed: (a) all pertinent studies on the anti-inflammatory effects of NPs in the management of IBD were identified; (b) the research methodologies used were described; (c) a thorough analysis explored the effects of NPs and their molecules on IBD; and (d) the molecular evidence on the effects of NPs and how they reduce IBD progression, oxidative stress, inflammatory reactions was examined. The period covered by the systematic review was from January 2011 to December 2022.

5.2. Eligibility criteria

The research effectively covered all articles written in English that were published between January 2011 and December 2022. A thorough search was conducted of the PubMed, Scopus, Web of Science, and Embase databases to identify the studies relevant to the research goal. The keywords “Inflammatory Bowel Disease,” “Medicinal Plants,” “Natural Products,” “Anti-inflammatory,” and “Ulcerative Colitis” were used in the search process. (a) Studies on laboratory animals treated with plant-based medicines for experimentally-induced IBD were included; (b) Studies with data on antioxidant enzymes, cytokines, IL-mediated signaling markers, diarrhea scores, and biomarkers connected to inflammatory responses were chosen for the next screening phase; (c) Research from every country or region worldwide was chosen; (d) In-vitro research was disregarded in cases where there were few or very few human trials on using natural remedies to treat IBD; (e) We only chose peer-reviewed research articles; (f) Studies that included review articles and chapters where it took more work to get all the information or where the approaches were deemed questionable, were not included. Papers that used figures to describe inflammatory response values without supplying numerical data were also excluded. This systematic review used the preferred reporting items for systematic reviews and meta-analyses (PRISMA) checklist [25,26].

5.3. Data gathering procedure

Fig. 1 shows a PRISMA flow diagram which illustrates the study's methodology and the criteria for accepting or rejecting publications. The only papers included were those that addressed the objectives of this review. The references of the selected studies were searched manually to identify any relevant articles not found in the database search.

5.4. Data extraction

The information taken from the research publications included the authors' names, the publication year, the study region, the type and strains of animals used in the study, the study type, the evaluation methods used, the level of exposure to NPs, and the standards and procedures followed to estimate biochemical markers, results, and putative mechanisms. The papers were initially independently assessed, and any discrepancies were settled by consulting.

6. Results and discussion

6.1. Search results

The systematic study included in vivo studies examining natural agents' potential anti-inflammatory therapeutic effects against IBD. In the initial search, 1,878 articles were found, but 1,040 of these were eliminated after thorough screening and analysis for the following reasons: (a) research unrelated to the goals and purposes of this systematic review; and (b) studies that were found to be reviews, editorials, conference proceedings, or meta-analyses. There were 112 duplicates among the 838 remaining articles, which were removed, leaving 762 articles. After independently assessing the titles and abstracts of these 726, the full texts of the 89 articles that met the review's eligibility criteria were read and included in the review.

6.2. Assessment of selected studies

Tables 1 and 2 present a summary of the findings detailing the preventative properties exhibited by plant extracts, standardized herbal formulations, and natural compounds in mitigating IBD in animal model studies [1,21,27–57,59–113]. About seventy-two investigations have been conducted on herbal extracts and their preparations, and twenty-four on pure molecules (Fig. 2) obtained from herbs. In these studies, mice and rats of both sexes were used. The majority of the investigations used mouse models. Mice are frequently used as models because of their similar immune systems, genes, and intestinal development to humans.

Mice belonging to the strains of C57BL/6, BALB/c, ICR, and CD1 were used, with C57BL/6 being the most commonly used. Among the rats, the Wistar albino strain was most commonly chosen, followed by Sprague Dawley rats. Dextran sodium sulfate (DSS), acetic acid (AA), 2,4,6-trinitro benzene sulfonic acid (TNBS), and 2,4-dinitro benzene sulfonic acid (DNBS) were used to induce UC or IBD in the animal models. The most frequently used model was the DSS-induced colitis model, followed by AA, TNBS, and DNBS. DSS, a synthetic sulfated polysaccharide composed of dextran and sulfated anhydroglucose units, is characterized by a high molecular weight and a branched-chain polysaccharide polymer of D-glucose that is highly soluble in water and forms a viscid gelatinous material. Most of the studies came from China, followed by South Korea, Nigeria, Egypt, Thailand, Indonesia, Brazil, India, the United States, Spain, and the United Arab Emirates.

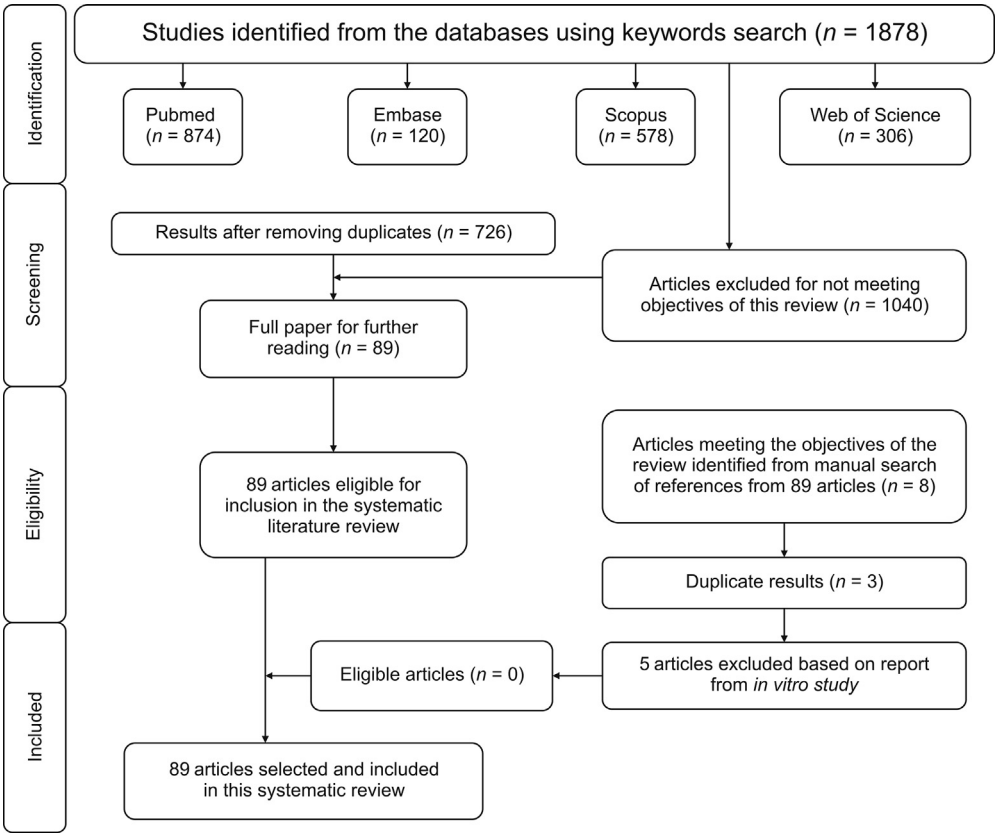

Fig. 1. Flowchart showing the search and article evaluation process using the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.

6.3. Effect of plant extracts and their preparations on interleukins and other inflammatory mediators in IBD

The spread of IBD, a chronic inflammatory disorder marked by ongoing inflammation of the intestinal lamina propria, is a significant public health concern. The pathogenesis of IBD includes genetic predisposition, immune response, and environmental stressors [6]. As was shown by Lin et al. [21], aqueous extract from *Bruguiera gymnorrhiza* (L.) Rhizophoraceae had the ability to decrease inducible nitric oxide synthase (iNOS) levels and modulate the inflammatory cytokines TNF-α, INF-γ, IL-6, and IL-1β, among other inflammatory and oxidative stress markers [21]. The ability of *Telfairia occidentalis* Hook. F. (Cucurbitaceae) aqueous leaf extract (TO) to mitigate DSS-mediated colitis in rats was investigated. TO's impact on inflammation, preclinical characteristics, including disease activity index (DAI), and microscopic and macroscopic changes to the colonic mucosa were investigated. TO significantly increased the levels of IL-1, IL-6, and TNF-α, reducing the DSS-mediated inflammation in rats' colons [27]. IBD is already widespread, creating severe health issues for people, with a heavy financial impact on society. In conclusion, researching and finding challenging NPs for IBD is most needed since synthetic drugs have severe adverse side effects [28].

Actinidia arguta (Siebold & Zucc.) Planch. Ex Miq. (Actinidiaceae), a freeze-dried fruit powder, was studied for its anti-inflammatory role against UC in rats. The study reported that it reduced the pathological changes in UC, colon and spleen inflammation, and immunological suppression. It dramatically diminished oxidative stress and inflammatory markers, particularly MPO. In addition, it played a broader role in downregulating the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α along with activation of p38, c-Jun N-terminal kinase (JNK), and extracellular signal-regulated kinase (ERK). *A. arguta* reduced the symptoms of UC and the inflammatory response through activating the mitogen-activated protein kinase (MAPK) pathway [29].

A combination of methanolic extract of Egyptian propolis and *Moringa oleifera* Lam. (Moringaceae) prevented UC in AA-induced colitis complications. It inhibited COX-1 and COX-2 enzymes and reduced the ulcerative index, lesion score, oxidative indicators, and inflammatory mediators. Both extracts were synergistically effective against UC [30]. Pomegranate (*Punica granatum* L., Punicaceae) juice, rich in antioxidants and phytochemicals, has been shown to effectively reduce rat inflammation. The juice was tested to assess its prophylactic and therapeutic anti-inflammatory effects against UC and was found to reduce inflammation, necrosis, and colonic damage. It also reduced the levels of MPO, C-reactive protein (CRP), alkaline phosphate (ALP), and fibrinogen (Fb), and increased glutathione (GSH) content. The lowering of inflammatory biomarkers, such as MPO and CRP, and the increased GSH contributed to the anti-inflammatory effect of the pomegranate juice [31].

A study conducted by Guo et al. [32] reported that treatment with ginger preparation ameliorated UC in mice and reduced the DAI score, lowered body weight loss, reduced shortening of colon length, IL-6 and iNOS and improved spleen index, resulting in a reduction in the severity of the mucosal injury. Moreover, ginger treatment regulated the intestinal flora [32]. *Perilla frutescens* (L.) Britton (Lamiaceae) extract attenuated inflammation in DSS-induced mice colitis by reducing body weight loss, diarrhea, blood stool, epithelium damage, shrinkage and colon thickening.

Table 1
Inflammatory bowel disease (IBD) animal models treated with herbal substances and standardized plant extracts are outlined.

Natural products	Animal/strains	Dose/route	Effects and molecular mechanisms	Refs.
Aqueous extract of *Bruguiera gymnorrhiza* (L.) Lam fruit (Rhizophoraceae)	BALB/c mice	25, 50 and 100 mg/kg Oral	↓ MDA, TNF-α, IL-6, IL-1β, and IFN-γ; ↑ IL-10; ↑ SOD and GSH; ↓ iNOS and COX-2; ↑ protein level of Nrf2 and mRNA levels of GCLC, GCLM, HO-1 and NQO1; ↓ expression of Keap1 and cytosolic Nrf2	[21]
Aqueous leaf extract of *Telfairia occidentalis* Hook. f. (Cucurbitaceae)	Wistar rats	200 mg/kg Oral	↓ NO, MPO, TNF-α, IL-1β, and IL-6; ↑ the activities of SOD, CAT and GST; ↓ DAI score	[27]
Freeze-dried fruit powder of *Actinidia arguta* (Siebold & Zucc.) Planch. ex Miq. (Actinidiaceae)	BALB/c mice	300 and 600 mg/kg	↓ oxidative stress levels; ↓ MPO and proinflammatory cytokines (IL-1β, IL-6 and TNF-α); ↓ p38, JNK and ERK	[29]
Moringa oleifera Lam. (Moringaceae) seeds methanol extract (MOSME) and *Egyptian propolis* methanol extract	Sprague Dawley rats	MOSME: 100 and 200 mg/kg; propolis methanol extract: 50 and 100 mg/kg; MOSME + propolis: 100 + 50 mg/kg Oral	↓ inflammatory mediators TNF-α and NO; ↓ oxidative markers (MPO and MDA)	[30]
Pomegranate juice	Wistar rats	2, 5 and 8 mL/kg	↓ inflammation and necrosis; ↓ MPO level; ↑ GSH; ↓ ALP, CRP and Fb	[31]
Ginger preparations	BALB/c mice	500 mg/kg Oral	↓ IL-6 and iNOS; ↓ inflammatory cell infiltration and altered the intestinal microbiomes of colitis mice; ↓ DAI score; ↑ body weight	[32]
Perilla frutescens (L.) Britton extract (PE) (Lamiaceae)	ICR mice	20 and 100 mg/kg Oral	↓ expression of COX-2, iNOS and cyclin D1; ↓ NF-κB, STAT3 expression; ↑ HO-1 and Nrf2 expression; ↑ body weight	[33]
Purple-fleshed potato (raw or baked)	Pigs	HCD supplemented with 10% of purple-fleshed potato (raw or baked)	↓ IL-6 expression; ↓ IL-1α and Map2k1	[34]
Methanolic extract of *Lagerstroemia speciosa* (L.) Pers (Lythraceae) leaves (LS)	C57BL/6 mice	100 and 200 mg/kg Oral	↓ MDA; ↑ SOD, CAT and GSH; ↓ DAI score; ↑ body weight	[35]
Ethyl acetate extract and polyphenol extract from cranberry fruits	CD-1 mice	0.1% PPE and 0.05 EPE Oral	↑ body weight and colon length of the colitis animals; ↓ mRNA expression of IL-1β, IL-6, and TNF-α	[36]
Butanol extract from *Acacia saligna* (Labill.) H.L. Wendl (Fabaceae)	Wistar rats	100 mg/kg Oral	↓ COX-2, PGE2 and IL-1β levels	[37]
Ethanol extract from *Hibiscus sabdariffa* L. (Malvaceae)	Albino mice	300 mg/kg	↑ anti-inflammatory cytokine (IL-10); ↓ the synthesis of pro-inflammatory cytokines (IL-6 and TNF-α)	[38]
Ethyl acetate extract of *Baccharis dracunculifolia* DC. (Asteraceae)	Wistar rats	5, 10, 25, 50, 100 and 200 mg/kg Oesophageal catheter	↓ colon damage score and lesion extension; ↓ diarrhea signs; ↑ GSH content; ↓ MPO and ALP activities	[39]
Green and dark tea extract	C57BL/6 mice	5 mg/kg Oral	↓ TLR4/MyD88/NF-κB pathway; ↑ body weight	[40]
Polyphenolic extract from *Aristotelia chilensis* (Mol.) Stuntz (Elaeocarpaceae)	BALB/C mice	50 mg/kg Oral	↓ transmural inflammation; ↓ expression of inflammatory proteins COX-2 and iNOS; ↑ Nrf2/HO-1 pathway; ↑ body weight; ↑ colon length	[41]
Fresh Saengshik (FSS) with heated Saengshik (HSS), a traditional Korean health food contains freeze-dried whole grain, fruit, and vegetable powder	C57BL/6J mice	A diet with a 30% or 70% of FSS and HSS	↓ TNF-α and IL-1β; ↓ colonic mRNA expression level of inflammation-related iNOS and COX-2; ↓ colon shortening; ↑ body weight	[42]
Grape peel powder (GPP); extractable polyphenols (EP); dietary fiber and non-extractable polyphenol-rich fraction (NEP-F); polyphenols-poor, fiber-rich residue (FR)	Wistar rats	GPP – 80 g/kg in feed; EP – 198 mL/kg in feed; NEP-F – 21.7 g/kg in feed; FR – 3.5 g/kg in feed	↓ TNF-α and IL-1β; ↓ the m-RNA expression levels of TNF-α, IL-1β, IL-6 and NF-κB	[43]
Grape Seed Meal (GSM)	TOPIG hybrid pigs	8% GSM Oral	↓ TNF-α, IL-1β, IL-6, IL-8 and IFN-γ; ↑ IL-10 and TGF-β; ↓ Colony-stimulating factors GCSF and GM-CSF, IL-6sR, sTNF-RI; restored MAPK genes (p38α, JNK1, JNK2, ERK2); ↓ mRNA levels for Akt2, Akt3 and p70S6K; ↓ NF-κB1 (NF-kB/p50); ↓ RELA (NF-κB/p65) and NEMO	[44]
Aloe vera L. (Asphodelaceae) extract	BALB/C mice	200 mg/kg Oral	↓ score of neutrophilic infiltration; ↓ iNOS, MPO, and pro-inflammatory cytokines (TNF-α and IL-6); ↑ IL-10; ↓ expression of NF-κB	[45]

(*continued on next page*)

Table 1 (*continued*)

Natural products	Animal/strains	Dose/route	Effects and molecular mechanisms	Refs.
Functional yogurt based on *Malva parviflora* L. (Malvaceae) ethanol extract nanoemulsion	Wistar rats	100 mg/kg Oral	↑ colon GSH and CAT; ↓ colon TBARS; ↓ TNF-α, IL-6, NF-κB and Hcy	[46]
Pennyroyal phenolic extract	CD-1 mice	15 mg/kg Oral	↑ antioxidant status; ↓ expression of COX-2 and iNOS	[47]
Mother tincture	CD-1 mice	5, 25 and 50 mg/kg Oral	↓ immune histochemical expression of the inflammation markers IL-6 and TNF-α; ↑ MDA and GSH	[48]
Red lentil powder	C57Bl/6 mice	A basal diet-supplemented diet with 5, 10 or 20% of red lentil powder Oral	↑ mRNA expression of SCFA receptors GRP 41 and 43; ↑ tight/adherens junction proteins (ZO-1, Claudin-2, E-cadherin); ↓ intestinal inflammation	[49]
Fresh fruit juice of *Opuntia dillenii* Haw (Cactaceae)	Wistar rats	2.5 and 5 mL/kg Oral	↓ MPO, MDA, LDH; ↑ colonic levels of GSH	[50]
Probiotic *Bacillus coagulans* MTCC 5856 spores and prebiotic whole plant sugar cane fiber (PSCF)	C57BL/6J mice	4 g chow mash supplemented with probiotic *B. coagulans* MTCC 5856 spores (2×10^9 CFU/day/mouse); PSCF (200 g/day/mouse)	↓ pro-inflammatory cytokines (IL-1α, IL-1β, IL-6, IL-12, TNF-α and IFN-γ); preserved the tight junction protein-ZO-1, occludin, and claudin-1 expressions; ↓ DAI score	[51]
Camellia oil (*Camellia oleifera* Abel.) (*Theaceae*)	Sprague Dawley rats	2 mL/kg Gastric gavage	↑ SOD, CAT, GSH, GPx; ↓ LPO; ↓ pro-inflammatory protein production	[52]
Polyphenol-rich extract of *Ocimum gratissimum* L. leaf (Lamiaceae)	Wistar rats	200, 400 and 800 mg/kg	↓ IL-6, TNF-α, MPO, NO, COX-2 and MDA; ↑ IL-4, IL-10, SOD, CAT, GSH; ↓ DAI score	[53]
Methanol extract of *Bidens pilosa* L. (Asteraceae)	Wistar rats	100, 200 and 400 mg/kg	↑ colonic lipid peroxidation level; ↑ leukocytes infiltration; ↑ TNF-α level; ↓ colon damage	[54]
Ziziphus jujuba Mill. (Rhamnaceae)	C57BL/6 mice	5% and 10% diet Oral	↓ NF-κB/IL-6/JAK1/STAT3 signaling pathway; ↓ DAI score; ↓ colon shortening	[55]
Nanoparticles derived from edible ginger (GDNPs 2)	FVB/NJ and C57BL/6 and IL10−/− mice	0.3 mg/mouse Oral	↓ proinflammatory cytokines TNF-α, IL-6 and IL-1β; ↑ anti-inflammatory cytokines IL-10 and IL-22	[56]
Bioactive fraction of *Turbinaria ornata* Turner (Sargassaceae)	C57BL/6 mice	15 mg/kg Oral	↓ COX-2, TNF-α, and p-STAT3; ↑ FOXP3 and Treg expression; ↑ Th1 and Th2 transcription factor	[57]
Summer savory	CD-1 mice	15 mg/kg Oral	↓ iNOS and COX-2 expression	[59]
Xique-Xique juice	Wistar rats	5 and 10 ml/kg Oral	↓ TNF-α and IL-1β; ↓ IL-17, NF-κB, and iNOS; ↑ SOCs-1, ZO-1, MUC-2; ↓ DAI score	[60]
Ethanol extracts from *Pycnoporus sanguineus* (L.) Murrill (Polyporaceae)	BALB/C mice	100, 200 and 400 mg/kg Oral	↑ mucosal integrity; ↑ expression of tight junction and adherens junction proteins in the colon; ↑ ZO-1, occludin, claudin-1, and E-cadherin; ↓ Th cells in the colon; ↓ Th cell-related cytokines (IL-6, IL-12, p40, IL-15 and TNF-α); ↓ DAI score; ↑ body weight; ↑ colon length	[61]
Chinese dragon's blood (CDB), a dark red resin extracted from *Dracaena cochinchinensis* (Lour.) S.C. Chen (Asparagaceae)	BALB/C mice	1.1 g/kg Intragastric	↑ expression of the mTOR, p-mTOR and p70S6K proteins; ↓ expression of the Akt, and p-Akt, there by repairing intestinal mucosal damage via the RSK/TSC2/mTOR/ribosome pathway; ↑ body weight; ↑ colon length	[62]
Mahkota Dewa fruit pericarp extract	Swiss Webster mice	650, 1,250, 2,500, and 5,000 mg/kg Oral	↓ inflammation score; ↓ iNOS expression in the cytoplasmic fraction of epithelial crypt.	[63]
Passiflora edulis Sims (Passifloraceae) peel flour	C57BL/6 mice	40 mg/kg	↓ IL-1β, IL-6 and IL-17; ↓ expressions of MCP-1 and ICAM-1; ↑ MUC-2 and MUC-3 expressions; ↓ expressions of MMP-2 and MMP-9	[64]
Chestnut shell extract	Zebrafish	4 μg/d/zebrafish Oral	↓ TNF-α and COX-2; ↑ IL-10	[65]
Aqueous and methanol extracts of *Amorphophallus paeoniifolius* (Dennst.) (Araceae) Nicolson tubers	Wistar rats	250 and 500 mg/kg Oral	↓ ALP, LDH and MPO activity; ↓ IL-1β and IL-6 in colon tissue; ↑ body weight; ↑ colon length	[66]
Salvia officinalis L. (Lamiaceae) leaves decoction extract	Wistar rats	50, 100 and 200 mg/kg Oral	Restored the levels and activities of MDA, H_2O_2, SOD, CAT and GPx in colonic mucosa; ↓ plasma CRP level and ALP activity	[67]
Ethanolic extract (EtOHE) and its hexane phase (HexP) obtained from the leaves of *Combretum duarteanum* (Cd) Cambess (Combretaceae)	Wistar rats	31.25, 62.5, 125, and 250 mg/kg Oral	EtOHE and HexP caused ↓ MPO and ↑ SOD activity; ↓ TNF-α and IL-1β; ↑ anti-inflammatory cytokine IL-10; ↓ expression of COX-2 and PCNA; ↑ colon length	[68]

(*continued on next page*)

Table 1 (*continued*)

Natural products	Animal/strains	Dose/route	Effects and molecular mechanisms	Refs.
Ricinus communis L. (Euphorbiaceae) root extract	Sprague-Dawley rats	250 and 500 mg/kg Oral	↓ inflammatory reaction; ↓ MPO, MDA and NO level; ↑ SOD activity; ↑ body weight; ↓ colon shortening	[69]
Rosemary extract	C57BL/6 mice	10 and 100 mg/kg Oral	↓ Sestrin 2 upregulation; improved barrier integrity; ↑ expression of ZO-1	[70]
Anthocyanin-rich purple-fleshed potato	C57BL/6 mice	150 and 250 g/kg Oral	↓ intestinal permeability; ↓ colonic MPO activity; ↓ IL-6 and IL-17 expression in colon tissue; ↓ IL-1β; ↑ colon length	[71]
Rhodiola crenulata (HK. f. *et*. Thoms) H. (Crassuloideae) Ohba root extract	C57BL/6J mice	125, 250 and 500 mg/kg Oral	↓ IL-1β and IL-6; ↓ expressions of TNF-α, and IL-6 in the colon; ↑ expressions of ZO-1 and occludin in the colon and regulate gut microbiome; ↑ colon length	[72]
Xian-He-Cao-Chang-Yan formula	C57BL/6J mice	2.5, 5 and 10 g/kg	↓ F4/80 expression; ↓ phosphorylation of ERK; ↓ IL-6 and IL-1β mRNA expressions; ↓ $F4/80^{+}CD11c^{+}$cells; ↓ levels of pro-inflammatory cytokines; ↓ DAI score; ↑ colon length	[73]
Improved *Glycyrrhiza* variety, Wongam	BALB/c mice	10, 50 and 100 mg/kg Oral	↓ inflammatory mediators such as IL-6, TNF-α, and PGE2; ↓ DAI score; ↑ body weight; ↑ colon length	[74]
Ethanolic extract of *Garcinia mangostana* L. (Clusiaceae) (GM) and its active constituent α-mangostin	ICR mice	GM at 40, 200 and 1,000 mg/kg Oral α-mangostin at 30 mg/kg Oral	↓ mast cell infiltration, MPO activity, NO, and MDA production; ↑ catalase and SOD activity; ↓ mRNA expressions of TNF-α, TLR-2, ICAM-1, VCAM-1, and MCP-1; ↓ DAI score; ↑ colon length	[75]
Black rice bran extract plus β-glucan supplementation	Wistar rat	500 mg/kg Oral	↓ MDA level; ↓ CAT, SOD and GPx levels; ↓ IL-6, IL-17, and IFN-γ level and ↑ IL-10, TGF-β; ↑ body weight	[76]
Polyphenolics-rich mango extract	Sprague-Dawley rats	89.74 mg/kg Oral	↓ expression of IL-1β mRNA, TNF-α, IL-1β, and IL-6 in the intestinal mucosa; ↓ expression of iNOS, COX-2, PI3K, mTOR, p70S6K, and HIF-1α mRNA; ↓ the protein expression of PI3K (p85b); ↓ expression of total and phosphorylated Akt; ↓ mTOR, p70S6K protein, RPS6 total protein, and HIF-1a; ↑ miR-126	[77]
Zanthoxylum bungeanum Maxim. (Rutaceae) pericarp extract (ZBE)	C57BL/6 mice	0.5, 1 and 2 g/kg Oral	↓ colonic expression of TNF-α, IL-1β and IL-12 via the regulation of TLR4 and related pathways; ↓ NF-κB p65 and IκBα phosphorylation levels; ↓ protein phosphorylation of three MAPKs (P38, ERK, and JNK); ↑ body weight; ↑ colon length	[78]
Prunus mume Siebold & Zucc. (Rosaceae) fruit juice fermented with *Lactobacillus* strain	ICR mice	100 and 200 mg/kg Oral	↓ levels of IL-6, IL-12, IL-1β, IL-17 and TNF-α; ↓ shortening of colon length	[79]
Aerial parts of *Jasminum grandiflorum* L. subsp. (Oleaceae)	Wistar rats	100, 200 and 400 mg/kg Oral	↓ INF-γ, TNF-α, IL-6 & IL-1β; ↓ MPO and MDA; ↓ expression of NF-κB-p65; ↓ TNF-α and caspase-3	[80]
Plant extracts of *Atractylodes macrocephala* Koidz (Asteraceae) (AM) or *Taraxacum herba* (TH) (G.H. Weber ex Wiggers) (Asteraceae)	C57BL/6 mice	AM 100 mg/kg; TH 100 mg/kg; AM + TH; 50 mg/kg Oral	↓ COX-2, iNOS, IL-1β and TNF-α mRNA expression; ↓ F4/80 and CD3; ↓ NF-κB and STAT3; ↑ HO-1 expressions and ↓ NF-κB	[81]
Ethanol leaves extract of *Aster glehni* Fr. Schm. (Asteraceae)	ICR mice	25 and 50 mg/kg Oral	↓ TNF-α, IL-1β, and IL-6 production; ↓ COX-2 and iNOS expression; ↓ activation of NF-κB; nuclear translocation of p65 NF-κB subunit, phosphorylation and degradation of IκBα; ↓ DAI score	[82]
Ethanolic extract of rhizome of *Curcuma xanthorrhiza* Roxb. (Zingiberaceae) and xanthorrhizol	BALB/c mice	4 and 40 mg/kg Oral	↑ S100a8 and IL-1β expression; ↓ TNF-α and IL-6 expression; ↓ NF-κB and ↓ the expression of COX-2; ↓ DAI score; ↑ colon length	[83]
Muscadine grape phytochemicals (MGP) and muscadine wine phytochemicals (MWP)	C57BL/6J mice	MGP or MWP 500 mg/kg Oral	↓ MPO activity and IL-1β, IL-6, and TNF-α; alleviated inflammation via modulation of the NF-κB pathway; ↓ DAI score; ↑ intestinal health; ↑ body weight	[84]
Sugar cane extract (SCE)	ICR mice	1% SCE supplemented in basic diet Oral	Regulated colonic infiltration of inflammatory cells; ↓ IL-17; ↑ mRNA expression of SOD1; ↑ protein expression of occludin and claudin1; ↑	[85]

(*continued on next page*)

Table 1 (*continued*)

Natural products	Animal/strains	Dose/route	Effects and molecular mechanisms	Refs.
			nuclear Nrf2 abundance and activated signals of the NF-κB p65 and Nrf2	
Persea americana Mill. (Lauraceae) ethanol extract	ICR mice	50, 100, or 200 mg/kg Oral	↓ expression of iNOS, COX-2, IL-6, IL-1β, TNF-α; ↓ DSS-induced activation of NF-κB and STAT3	[86]
Ethanol extract of *Veronica polita* Fr. (Plantaginaceae)	C57BL/6 mice	200 mg/kg Oral	↓ NO and MDA level; ↓ expression of TNF-α, IL-1β, IL-6, iNOS and COX-2 in the colon tissue; ↓ STAT3 and NF-κB thus ameliorated JAK2/STAT3 and NF-κB signaling pathways; ↓ DAI score; ↑ body weight; ↓ colon shortening	[87]
Graviola leaf extract	Wistar rats	100 mg/kg Oral	↓ NO, MDA, MPO activity; ↑ GSH; ↓ Bax, caspase-3, Wnt1; ↑ Smo and Gli1, Bcl-2	[88]
Hydroethanolic extract of *Bryophyllum pinnatum* (Lam.) Oken (Crassulaceae)	Wistar rats and C57BL/6J mice	250 and 500 mg/kg and 100 and 200 mg/kg Oral	↓ MPO, and TNF-α; ↓ gene expression of inflammatory and oxidative markers (TLR-4, MCP-1, MIP-2, ICAM-1, IL-1β, IL-6, and iNOS); ↑ expression of proteins involved in maintaining epithelial integrity (TFF-3, villin, ZO-1, occludin, MUC-2, and MUC-3)	[89]
Aqueous and methanol stem-bark extracts of *Alstonia boonei* De Wild. (Apocynaceae)	Wistar rats	125 and 250 mg/kg Oral	↓ release of inflammatory markers; ↓ MDA and NO levels; ↑ SOD, CAT, and GSH	[90]
Aqueous extract of *Ipomoea asarifolia* (Desr.) Roem. & Schult. (Convolvulaceae)	Wistar rats	25, 50, and 100 mg/kg Oral	↓ MPO activity; ↓ the gene expression of JNK1, NF-κB -p65, STAT3; ↓ the levels of TNF-α, IL-1β ; ↑ IL-10; ↓ NF-κB -p65, iNOS, IL-17; ↑ SOCs-1, MUC-2; ↓ DAI score	[91]

Akt: Ak strain transforming; ALP: alkaline phosphatase; Bcl-2: B-cell lymphoma 2; CAT: catalase; JNK: c-Jun N-terminal kinase; CRP: c-reactive protein; COX-2: cyclooxygenase 2; SOCs-1: cytokine signaling-1; DAI: disease activity index; ERK: extracellular signal-regulated kinase; Fb: fibrinogen; FOXP3: forkhead box P3; GRP: gastrin-releasing peptide; Gli1: glioma-associated oncogene homologue 1; GCLC: glutamate-cysteine ligase catalytic subunit; GCLM: glutamate-cysteine ligase modifier subunit; GSH: glutathione; GPx: glutathione peroxidase; GST: glutathione s-transferase; GCSF: granulocyte colony stimulating factor; GM-CSF: granulocyte macrophage colony stimulating factor; H_2O_2: hydrogen peroxide; HO-1: heme oxygenase-1; Hcy: homocysteine; HIF: hypoxia inducible factor; iNOS: inducible nitric oxide synthase; ICAM-1: intercellular adhesion molecule 1; INF-γ: interferon gamma; IL: interleukin; IL-1β: interleukin-1 beta; IL-1α: interleukin-1 alpha; IL-6sR: release of soluble IL-6 receptor; JAK: janus kinase; Keap1: kelch-like ECH-associated protein 1; LDH: lactate dehydrogenase; LPO: lipoxygenase; MIP-2: macrophage inflammatory protein-2; MDA: malondialdehyde; mTOR: mammalian target of rapamycin; miR-126: microRNA-126; Map2k1: mitogen-activated protein kinase 1; MAPK: mitogen-activated protein kinases; MCP-1: monocyte chemoattractant protein-1; MUC: mucin; MyD88: myeloid differentiation primary response 88; MPO: myeloperoxidase; NQO1: NAD(P)H quinone dehydrogenase 1; NO: nitric oxide; Nrf2: nuclear factor erythroid 2-related factor 2; NEMO: nuclear factor kappa B essential modulator; NF-κB: nuclear factor kappa beta; NF-κB-p65: nuclear factor kappa B-p65; IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; p70S6K: p70S6 kinase; PI3K: phosphoinositide 3 kinase; p-STAT3: phosphorylated signal transducer and activator of transcription-3; p-mTOR: phosphorylated mammalian target of rapamycin; PGE2: prostaglandin E2; Treg: regulatory T; RELA: REL associated protein; SCFA: short-chain fatty acid; STAT3: signal transducer and activator of transcription-3; Smo: smoothened; SOD: superoxide dismutase; S100a8: S100 calcium binding protein A8; sTNF-RI: human soluble tumor necrosis factor receptor I; Th: T helper; TLR: toll like receptor; TGF-β: transforming growth factor-β; TFF-3: trefoil factor 3; TSC2: tuberous sclerosis 2 proteins; TNF-α: tumor necrosis factor alpha; TBARS: thiobarbituric acid reactive substances; VCAM-1: vascular cell adhesion protein 1; Wnt1: Wingless/Int1; ZO-1: zonula occludens.

Additionally, the *P. frutescens* extract inhibited IκBα phosphorylation and degradation, p65 migration, NF-κB activity, STAT3 nuclear translocation, toll-like receptor (TLR) 4 signaling mediators, and oxidative stress resulting in a reduction in total inflammation [33].

Purple-fleshed potatoes reduced inflammation and colon carcinogenesis. They also downregulated IL-6, IL-1α and MAPK1 during the inflammatory cascade [34]. *Lagerstroemia speciosa* (L.) Pers. (Lythraceae) extract, which is rich in triterpenes, tannins, ellagic acids, glycosides, and flavones, ameliorated DSS-induced UC in mice. It reduced the DAI score, improved stool consistency and bleeding, prevented body weight loss and colon length shortening, reduced oxidative stress and restored the colon tissue architecture [35].

Cranberry ethyl acetate (EAE) and polyphenol extract from cranberry fruits exerted chemopreventive activity on mice colonic tumorigenesis. EAE contains proanthocyanins, triterpenes, and sterols. The polyphenol extract from cranberry consisted of polyphenols and triterpenes. The extract reduced the levels of the pro-inflammatory cytokines, TNF-α, IL-1β, and IL-6 in the colon tissue [36]. *Acacia saligna* (Labill.) H. L. Wendl. (Fabaceae) (ASBE) and its nano-formulation reduced cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), and IL-1β in rat colitis. ASBE nano-formulations also decreased the ulcer ratio, normalized histopathological changes, reduced intestinal mucosal lesions, decreased inflammatory infiltration, and increased PGE2 production [37].

A study by Lubis et al. [38] reported the inflammation-reducing effect of roselle petal extract (*Hibiscus sabdariffa* L. Malvaceae) on DSS-induced colitis in mice. The extract reduced TNF-α and IL-6, and increased IL-10 levels [38]. *Baccharis dracunculifolia* DC (Asteraceae) extract effectively improved experimental UC induced by TNBS in rats. The extract attenuated damage to the colonic mucosa, prevented colonic GSH depletion, inhibited lipid peroxidation and reduced MPO activity [39].

Liu et al. [40] reported the prebiotic effect of green and dark tea extracts against colitis in mice. Both extracts improved colitis-related symptoms such as colonic inflammation, loss of barrier integrity, gut microbiota dysbiosis, and body weight loss. Furthermore, the extracts downregulated the TLR4/myeloid differentiation primary response (MyD)88/NF-κB pathway [40]. *Aristotelia chilensis* (Mol.) Stuntz (Elaeocarpaceae) phenolic extract (Ach) in a

Table 2
IBD animal models treated with natural molecules are outlined.

Natural molecules	Animal/strains	Dose/route	Effects and molecular mechanisms	Refs.
Nerolidol, a monocyclic sesquiterpene from German Chamomile tea	Wistar rats	50 mg/kg Oral	↓ MDA formation; ↑ GSH, CAT, SOD activities; ↓ MPO activity; ↓ calprotectin, IL-1β, IL-23 and TNF-α; ↓ LOX-1/IL-1β and TLR4/NF-κB signaling and ↓ AMPK/Nrf2/HO-1 pathway; ↑ body weight	[1]
Dihydroberberine, an isoquinoline alkaloid	BALB/C mice	12.5, 25 and 50 mg/kg Oral	↓ TNF-α, IL-1β, IL-6, IL-17, and IFN-γ; ↓ TLR4 and MyD88; ↓ ratio of p65 (nucleus)/p65 (cytoplasmic) and p-IκBα/IκBα; ↓ TLR4/MyD88/NF-κB signaling pathway; ↓ DAI score	[28]
Sinapic acid	Kunming mice	10 and 50 mg/kg Intragastric	↓ Histological infiltration of inflammatory cells; ↓ MPO activity; ↑ SOD, GPx, and CAT; ↓ mRNA levels of TNF-α, IL-1β, IL-6, IL-17α, IL-18, and IFN-γ; ↓ activation of the NLRP3 inflammasome; ↓ expression of ZO-1, ↑ occludin, and claudin-1; ↑ body weight; ↓ colon shortening	[92]
Piceatannol (PIC)/caffeic acid phenethyl ester (CAPE)-loaded albumin nanoparticles (NP)	C57BL/6 mice	PIC: 20 mg/kg; CAPE: 20 mg/kg and PIC + CAPE loaded NP: 20 mg/kg Intraperitoneal	↓ cryptic epithelial damage and infiltration of inflammatory cells; ↓ INF-γ, IL-6, TNF-α and MPO expression; ↓ NF-κB; ↑ body weight; ↓ colon shortening	[93]
6-gingerol, 8-gingerol, and 10-gingerol from *Zingiber officinale* Rosc. (Zingiberaceae)	Sprague-Dawley rats	30 mg/kg Intraperitoneal	↑ SOD activity; ↓ MDA levels and MPO activity in the colon tissue; ↓ TNF-α and IL-1β levels; ↓ DAI score; ↑ body weight	[94]
Quercetin	C57BL/6 mice	100, 500, 1,000 and 1,500 ppm Oral	↑ colon length; ↑ GSH level, liver SOD and CAT activities; ↑ body weight	[95]
Cannabidivarin	CD1 mice	0.3–10 mg/kg Intraperitoneal and 0.3–30 mg/kg Oral	↓ mRNA levels of IL-1β, IL-6; ↑ colonic mRNA expression of the chemokine, MCP-1; ↓ TRPA2; ↑ body weight; ↓ colon shortening	[96]
75 kDa phytoglycoprotein isolated from *Cudrania tricuspidata* (Carr.) Bur. ex Lavallee. (Moraceae)	ICR mice	10 and 20 mg/kg Oral	Restored the expression level of cyclin D1, cyclin E, and CDK 2/4; ↓ DAI score; ↓ colon shortening	[97]
Menthol	C57BL/6 mice	1, 1.5 and 2 g of menthol per 100 g of normal diet	↓ expression of proliferation biomarkers β-catenin and Ki67 and ↓ IL-6, TNF-α and MPO; ↓ immune cells infiltration; ↑ colon length	[98]
Cinnamaldehyde (CA)	Wistar rats	2, 4 and 8 mg/kg Oral	↓ expression of TLR-4; ↓ TNF-α, MPO, and IL-6; ↓ neutrophil infiltration; ↓TLR-4 expression	[99]
Plant sterol esters (PSE) incorporated into a non-puffed extruded food (NPE) model	BALB/C mice	PSE was added into NPE at four concentrations (0.0%, 0.7%, 1.4%, and 2.1%) Oral	↓ COX-2 expression; ↑ caspase-3, caspase-8, and caspase-9 expressions; ↑ chemopreventive activity; ↓ inflammation and ↑ activation of both intrinsic and extrinsic apoptosis pathway	[100]
Chitosan (CTS) and chito oligosaccharide (COS)	Juvenile turbots	7.5 g/kg (CTS diet) or 2 g/kg (COS diet) Oral	↓ the expression of IL-1β, IL-8 possibly by ↓ NF-κB, AP-1 and/or mitogen activated protein kinase pathways; ↓ MDA concentrations and ↑ levels of CAT, GPx, GSH and SOD; ↑ lysozyme, ACP activities and IgM concentration	[101]
Nerolidol	C57BL/6J mice	50, 100 and 150 mg/kg Oral	↑ MPO; ↑ neutrophil and macrophage mRNA expression; ↑ CXCL2 and CCL2; ↑ IL-1β, IL-6, and TNF-α; ↑ Nrf2; ↑ antioxidant enzymes activity (SOD, CAT, HO-1); ↑ SOD3 mRNA levels	[102]
Myricetin (3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-4chromenone)	Wistar rats	25 and 50 mg/kg Oral	↑ antioxidant enzymes; ↓ ameliorated cisplatin-induced lipid peroxidation; ↑ xanthine oxidase activity; regulated the level of inflammation markers (NF-κB), Nrf2, IL-6, and TNF-α	[103]
Eriocitrin	C57BL/6J mice	30 mg/kg Oral	↓ TNF-α, IL-1β, IL-6 levels; ↓ the expression of inflammatory markers MMP-9, COX-2, iNOS, and NF-κB p65	[104]
Quercetin	Sprague Dawley rats	100 mg/kg Oral	↑ p-ERK protein expression; ↓ caspase-3 protein levels thereby decreasing apoptosis	[105]
GB1a, an active component from *Garcinia Kola* Heckel (Clusiaceae) nuts	C57BL/6 mice	25, 50 and 100 mg/kg Oral	↓ IL-6, TNF-α, NF-κB p65, CCL5, CCL20 and CXCL1 expression; ↑ ZO-1 and occludin expression; ↑ Nrf2 and HO-1;	[106]

(*continued on next page*)

Table 2 (*continued*)

Natural molecules	Animal/strains	Dose/route	Effects and molecular mechanisms	Refs.
			↓ NF-κB-mediated pro-inflammatory signaling	
Crude polysaccharide preparation obtained from *Cynanchum wilfordii* Hemsley (Asclepiadaceae)	BALB/c mice	100 and 200 mg/kg Oral	↓ IL-6 and TNF-α; ↓ iNOS and COX-2 expression; ↓ NF-κB phosphorylation; ↓ NF-κB activation	[107]
Hyperoside, lonicerin, and luteolin	Wistar rats	25, 50 and 100 mg/kg Oral	↓ m-RNA expressions of PGE2, TNF-α, IL-1β, and CRP; ↓ expression of NF-κB	[108]
Crude polysaccharides from *Physalis pubescens* Linn. (Solanaceae)	C57BL/6 mice	50, 100 and 200 mg/kg Oral	↓ neutrophil infiltration; ↓ ICAM-1 and MCP-1 expression; ↓ expression of TNF-α, iNOS, and COX-2; modulate NF-κB/iNOS/COX-2 signal transduction pathway	[109]
Licorice flavonoids isolated from *Glycyrrhiza inflata* Batalin (Fabaceae)	C57BL/6 mice	50 and 100 mg/kg Oral	↑ expression of pro-apoptosis protein Bax; ↓ anti-apoptosis protein Bcl-2; ↑ expression of p53 and P21; ↓ expression of Cyclin D1; ↓ mRNA levels of IL-1β, IL-6, and TNF-α in colonic tissues; ↓ mRNA levels of iNOS and COX-2; ↓ activation of NF-κB and p53, and ↓ production of inflammatory cytokines and ↓ phosphorylation of JAK2 and STAT3	[110]
Feruloylated oligosaccharides	C57BL/6 mice	200 and 400 mg/kg Oral	↓ IL-23 and IL-6; ↑ TGF-β1	[111]
Quercetin and indol-3-carbinol (I3C)	C57BL/6JRj WT and C57BL/6 Ahr−/− mice	50 mg/kg quercetin and 20 mg/kg indol-3-carbinol (I3C) Oral	↓ MPO expression; ↓ RORγt; ↓ IgA expression; restored FOXP3 and CLDN1 expression	[112]
Nobiletin	CD-1 mice	0.05% in diet Oral	↓ iNOS expression; ↑ HO-1, NQO1; ↓ the expression levels of cyclin D, cyclin E, CDK6, CDK4 and CDK2; ↑ CDK inhibitors p21and p27; ↑ tumor suppressor p53	[113]

ACP: acid phosphatase; AMPK: AMP-activated protein kinase; CAT: catalase; CCL2: chemokine (C–C motif) ligand 2; CCL5: chemokine (C–C motif) ligand 5; CCL20: chemokine (C–C motif) ligand 20; CXCL1: chemokine (C–X–C motif) ligand 1; CXCL2: chemokine (C–X–C motif) ligand 2; CLDN1: claudin 1; CRP: c-reactive protein; CDK: cyclin dependent kinases; COX-2: cyclooxygenase 2; DAI: disease activity index; p-ERK: phosphorylated extracellular signal-regulated kinase; FOXP3: forkhead box P3; GSH: glutathione; GPx: glutathione peroxidase; HO-1: heme oxygenase-1; IgM: immunoglobulin; IgA: immunoglobulin A; iNOS: inducible nitric oxide synthase; ICAM-1: intercellular adhesion molecule 1; INF-γ: interferon gamma; IL: interleukin; IL-1β: interleukin-1 beta; JAK: janus kinase; LOX-1: lectin type oxidized LDL receptor 1; MDA: malondialdehyde; MMP-9: Matrix metalloproteinase 9; MCP-1: monocyte chemoattractant protein-1; MyD88: myeloid differentiation primary response 88; MPO: myeloperoxidase; NQO1: NAD(P)H quinone dehydrogenase 1; NLRP3: nucleotide-binding domain, leucine-rich-containing family, pyrin domain–containing-3; Nrf2: nuclear factor erythroid 2-related factor 2; NF-κB: nuclear factor kappa beta; NF-κB-p65: nuclear factor kappa B-p65; IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; p-IκBα: phosphorylated nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; PGE2: prostaglandin E2; STAT3: signal transducer and activator of transcription-3; SOD: superoxide dismutase; TLR4: toll like receptor 4; TGF-β1: transforming growth factor-β1; TRPA2: transient receptor potential vanilloid type-2; TNF-α: tumor necrosis factor alpha; ZO-1: zonula occludens.

TNBS-induced CD model reduced body weight loss, prevented shortening of the colon, and transmural inflammation. Additionally, it increased the recovery of the colonic mucosal architecture and its mucosecretory function. Ach also promoted the polarization of macrophages to the M2 phenotype and the downregulation of COX-2 and iNOS expression, regulating the nuclear factor erythroid 2-related factor/heme oxygenase 1 (Nrf2/HO-1) antioxidant pathway [41].

Song et al. [42] reported the anti-colitis activity of fresh Saengshik (FSS) along with warmed Saengshik (HSS) in a DSS-induced colitis model in mice. Supplementation with FSS and HSS promoted body weight and reduced colonic shortening. The FSS decreased the serum levels of TNF-α and IL-1β. Furthermore, it reduced iNOS and COX-2 levels [42]. Grape peel powder (GPP) containing phenolic compounds and dietary fiber increased antioxidant levels and reduced colonic inflammation. GPP reduced the colonic tissue's kappa kinase beta inhibitor and NO levels. In addition, it downregulated NF-κB and MPO activity [43]. In another study, Pistol et al. [44] reported an improvement in colonic activity following treatment with bioactive compounds derived from grape seed flour in pigs with DSS-induced colitis. It attenuated the inflammatory disorders by inhibiting MAPKs and reducing NF-κB, IL-10 and transforming growth factor-beta (TGF-β) [44].

A study by Ismaeil et al. [45] reported the ameliorative effect of *Aloe vera* (L.), Burm.f. (Asphodelaceae) and heat killed *Lactobacillus plantarum* L.137 (HK L.137) on DSS-induced colitis in mice. The *A. vera* and HK L.137 decreased high histological grade colitis, the levels of bloody diarrhea, NF-κB, iNOS, MPO, IL-6, and TNF-α, and increased IL-10 expression [45]. El-Naggar et al. [46] reported the protective effect of functional yogurt based on *Malva parviflora* L. (Malvaceae) leaf extract nano-emulsion in UC induced by AA in rats. The extract inhibited lipid peroxidation and prevented the formation of ROS [46]. Pennyroyal, a phenolic product of *Mentha pulegium* L. (Lamiaceae), reduced inflammation and colon damage in a UC mouse model. It also produced an antiproliferative effect on colon cancer cells, with reduced visible signs of colon damage and inflammatory cell infiltration, and downregulated iNOS and COX-2 expression. Additionally, it reduced the proliferative capacity of HT-29 cells [47].

Thuja occidentalis L. (Cupressaceae), also known as mother tincture, was shown to have effective antioxidant and anti-inflammatory properties in colitis. The tincture promoted the restoration of colonic mucosal architecture, and decreased inflammatory infiltrate, IL-6, TNF-α expression, and lipid peroxidation [48]. Graf et al. [49] reported that cooked red lentils, which are rich in non-digestible carbohydrates and phenolic compounds,

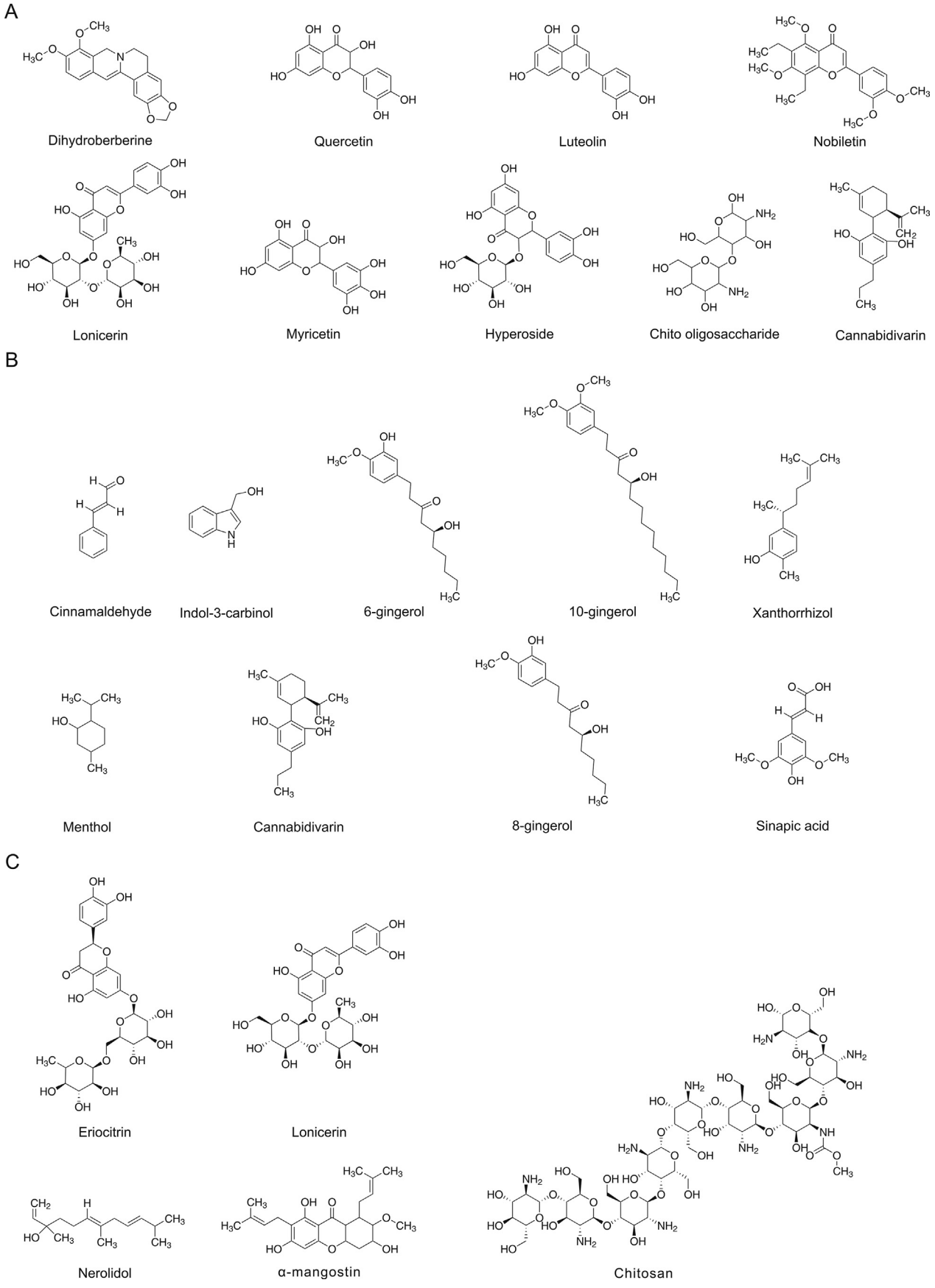

Fig. 2. Promising phytochemical structures identified or isolated from different plant species that significantly manage inflammatory bowel disease (IBD). (A) Phytochemical structures of plant polyphenols, alkaloids, and polysaccharides that significantly manage IBD. (B) Chemical structures of plant-derived phenolic compounds that effectively treat IBD. (C) Structures of polysaccharides, polyphenolic xanthonoid, sesquiterpene alcohol, and flavonoids substantially control the symptoms of IBD.

increased the abundance of short-chain fatty acid (SCFA) producing bacteria, fecal microbiota alpha diversity, fecal SCFA concentrations, zona occluden-1 (ZO-1), claudin (CLDN) 2 and E-cadherin, thereby improving intestinal health [49]. The fresh fruit juice of *Opuntia dillenii* (Ker Gawl.) Haw. (FJOD) had a protective effect on rat colitis. FJOD treatment improved intestinal damage, colon weight, and the clinical activity score. FJOD also reduced MPO, malondialdehyde (MDA), and serum lactate dehydrogenase (LDH) levels, and increased GSH in the colon [50].

A study by Shinde et al. [51] reported the effects of dietary supplementation with probiotic *Bacillus coagulans* MTCC 5,856 spores and prebiotic whole sugarcane fiber (PSCF) on DSS-induced colitis in mice, with supplementation reducing the DAI score and the colon histological score. Furthermore, *B. coagulans* and PSCF modulated serum IL-1β and CRP levels [51]. *Camellia* oil (CO), which is rich in bioactive phytochemicals, regulated intestinal microbiota composition and improved AA-induced colitis in rats. CO ingestion increased the Firmicutes/Bacteriodetes ratio, and the relative abundance of *Bifidobacterium*. CO also increased antioxidant enzymes, and reduced inflammatory damage and lipid peroxidation [52].

Alabi et al. [53] reported that the polyphenol-rich extract of *Ocimum gratissimum* L. (Lamiaceae) leaves (PREOG) reduced the production of pro-inflammatory cytokines and oxidative stress in a DSS-induced colitis model. PREOG also decreased DAI scores, IL-6, TNF-α, MPO, NO, COX-2, and MDA concentration[53]. The methanolic extract of *Bidens pilosa* L. (Asteraceae) decreased colonic lipid peroxidation and the macroscopic colonic damage score, maintained the colon weight/length ratio, and reduced leukocyte infiltration and TNF-α levels in TNBS-induced rat colitis. Furthermore, *B. pilosa* inhibited colonic GSH depletion, prevented mucosal ulceration and desquamation, and preserved the epithelial layer [54].

Periasamy et al. [55] reported the preventive effect of dietary *Ziziphus jujuba* Mill. (Rhamnaceae) on colitis-associated colorectal carcinogenesis in mice. *Z. jujuba* reduced fecal blood, diarrhea, DAI, spleen weight, and tumor count. It also inhibited the NF-κB/IL-6/JAK1/STAT3 signaling pathways, and increased colon length. Moreover, it also lowered inflammation and prevented the growth of colon cancers. The results of these studies indicate that NPs exhibit strong anti-inflammatory effects by inhibiting JAK1/STAT3 signaling in IBD. This might be related to an antioxidative mechanism that normalizes oxidative stress-stimulated biomarkers (Fig. 3).

6.4. Effect of standardized plant extracts on interleukins and other inflammatory modulators in IBD

Conventional treatments for IBD often involve anti-inflammatory agents and corticosteroids that can cause side effects, thus immunomodulators are a valuable alternative to these agents [56,57]. Standardized plant extracts have been studied as a possible alternative to conventional treatments for inflammatory diseases. These extracts contain bioactive compounds that can modulate the inflammatory response and have a lower risk of side effects. Some of these compounds have been identified as modulators of inflammatory signaling markers, thereby inhibiting the production of pro-inflammatory cytokines [58].

A study by Rocha et al. [59] showed that summer savory ethanolic extract, which is rich in hydroxycinnamic acids, flavonol glycosides, flavones and flavonones, and flavonols, attenuated colonic injury and inflammation in IBD mice, with summer savory ethanolic extract reducing colonic ulcer, severe diarrhea, and paw edema. The extract also reduced inflammatory markers, with a decrease in histological damage. Xique-Xique (*Pilosocereus gounellei* (F.A.C. Weber ex K.Schum.) Byles & G.D. Rowley (Cactaceae)) juice, which is rich in ash, and fibers, ameliorated AA-induced colitis in rats. The Xique-Xique juice treatment reduced the

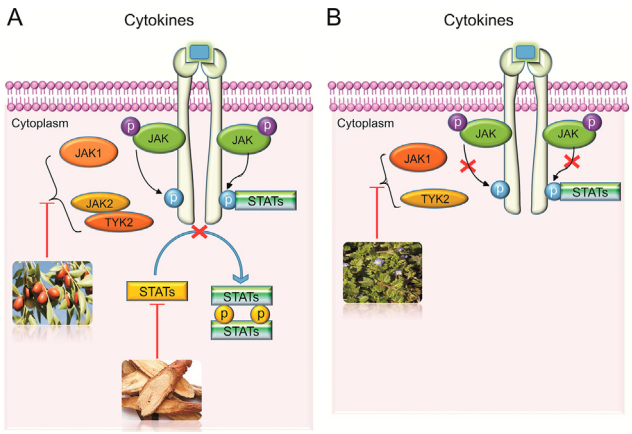

Fig. 3. Natural products (NPs) targeting the janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathways involvement in inflammatory bowel disease (IBD) development. (A) Licorice flavonoids targeting STAT proteins and inhibiting STAT, and preparations from dietary *Ziziphus jujuba* targeting JAK proteins. (B) Ethanol extract of *Veronica polita* inhibits the phosphorylation of JAK1 and downregulates the inflammatory reactions. TYK: human tyrosine kinase.

inflammatory process, and preserved crypts and goblet cells, reducing the DAI score and oxidative stress, GSH depletion and MDA levels. It also reduced TNF-α, IL-1β, IL-17, iNOS, and NF-κB pro-inflammatory markers, and increased mucin (MUC)-2 and ZO-1 gene expression [60].

Ethanolic extract of *Pycnoporus sanguineus* (L.) Murrill (Polyporaceae), which had ergosterol as a main component, effectively ameliorated DSS-induced colitis in mice. The extract treatment reduced body weight loss, DAI scores, colon length shortenings, and mucosal damage, such as edema, and preserved villi. The important cell adhesion proteins ZO-1, occludin, CLDN-1, and e-cadherin were upregulated following the extract treatment, while LPS was downregulated, indicating a reduction in endothelial damage. The inflammatory condition in the extract treated group was also ameliorated which was evidenced by the reduced proportion of Th cells, IL-12, IL-15, IL-6, and TNF-α cytokines, and lowered MPO activity. The capability of the extract in inducing apoptosis in Th cells in vitro was also evidenced, which indicates the positive inflammatory mediating activity of the extract [61]. Chinese dragon's blood (CDB), a crude substance from *Dracaena cochinchinensis* (Lour.) S.C. Chen. (Asparagaceae), ameliorated intestinal damage in acute UC. Pterostilbene and resveratrol are the major constituents of *D. cochinchinensis*. CDB reduced body weight loss, bloody stool, colonic mucosal damage, diarrhea and colon length shortening. In addition, it induced differentially expressed proteins in colonic tissue with an enrichment in the structural constituents of ribosomes and the ribosome pathway, upregulating the expression of the mammalian target of rapamycin (mTOR), phosphorylated-mTOR and p70S6K proteins. It downregulated the Ak strain transforming (Akt), p-Akt, and p4EBP1 protein expressions [62].

Kusmardi et al. [63] evaluated the anti-inflammatory effect of Mahkota dewa fruit pericarp extract (*Phaleria macrocarpa* (Scheff.) Boerl. Thymelaeaceae), which is rich in flavonoids and saponin. The extract also reduced inflammatory infiltrate and iNOS expression [63]. *Passiflora edulis* Sims (Passifloraceae) peel, which is rich in C-glycosyl flavonoids such as isoorientin, vicenin, orientin, and isovitexin reduced infiltration and damage to the mucosal barrier, decreasing the pro-inflammatory cytokines IL-1β, IL-6, and IL-17. It also downregulated the monocyte chemoattractant protein 1 (MCP-1), the intercellular adhesion molecule 1 (ICAM-1) and metalloproteinase (MMP)-2 and MMP-9, as well as improving MUC-2 and MUC-3 expression [64]. Chestnut shell (*Castanea sativa*

Mill. Fagaceae) extract is rich in tannins and has anti-inflammatory properties, improving dysbiosis in a zebrafish model. The extract enhanced the k-carrageenan-induced damage of the fish's gut, decreased TNF-α and COX-2, and elevated the anti-inflammatory cytokine IL-10. It also enhanced the growth of the beneficial bacteria *Enterobacteriaceae* and *Pseudomonas* [65].

The tuber of *Amorphophallus paeoniifolius* (Dennst.) Nicolson (Araceae) extract, which is rich in betulinic acid and β-sitosterol, reduced AA-induced UC in rats. It reduced body weight loss and diarrhea, and preserved colon weight/length ratio in rats. It also reduced the ulcer score and ulcer index in colonic tissue. The extract also improved the phosphohydrolase, MPO, LDH, lipid peroxidase, superoxide dismutase (SOD), catalase (CAT), IL-1β and IL-6 levels. Additionally, the extract lowered tissue necrosis and hemorrhage [66]. *Salvia officinalis* L. (Lamiaceae) extract contains a high proportion of polyphenols, flavonoids and total tannins. The extract also reduced hemorrhagic lesions, edema and necrosis, and ameliorated the congestion of cells, alterations in the surface coating and inflammatory cell infiltration. Additionally, MDA and hydrogen peroxide levels were downregulated with increased antioxidant enzyme status [67].

De Morais Lima et al. [68] reported the anti-inflammatory effect of ethanolic extract and the hexane part of *Combretum duarteanum* Cambess (Combretaceae) in a colitis mouse model. The extract, comprising triterpenes, reduced the ulcerative lesion area, the lesion score, colon weight/length ratio, diarrhea, tissue damage, inflammatory cell infiltration, MPO activity, TNF-α, IL-1β and COX-2 levels, the anti-proliferative cell nuclear antigen and anti-SOD expression. Additionally, it increased IL-10 levels along with increased spleen size [68]. *Ricinus communis* L. (Euphorbiaceae) root extract contains carbohydrates, glycosides, saponins, flavonoids, alkaloids, tannins and phenolic compounds. The extract increased body weight, decreased stool consistency score, suppressed inflammation and mucosal damage, and minimized colon shortening in a rat model of colitis. The extract also reduced MPO and NO levels, and increased SOD activity [69].

Veenstra et al. [70] reported that rosemary extract containing carnosic acid and carnosol increased ZO-1 protein improved DAI, and suppressed sestrin 2 upregulation with reduced cellular stress and improved intestinal barrier integrity. Purple-fleshed potato, which is rich in anthocyanin, reduced DSS-induced mice colitis. It also reduced the shortening of colon length, liver hypertrophy, splenomegaly, epithelial damage, IL-6, IL-17, IL-1β, flagellin protein, as well as suppressing MPO activity. In addition, it raised the relative amount of the beneficial bacteria *Akkermansi muciniphila*, and reduced pathogenic bacteria, such as, *Escherichia coli* and *Enterobacteriaceae* [71].

Rhodiola crenulata (Hook.f. & Thomson) H. Ohba (Crassulaceae) extract has 63 constituents comprising flavonoids, benzyl and phenol derivatives, phenylpropanoids, acyclic alcohol derivatives, organic acids and alkaloids. The extract increased colon length, decreased the inflammatory cytokines IL-1β and IL-6, and reduced the expressions of TNF-α, IL-1β and IL-6 in DSS-induced colon tissue. The extract also inhibited apoptotic cells in colons, regulated intestinal barrier function, and reduced the gut permeability with increased microbial diversity [72].

Xian-He-Cao-Chang-Yan formula (XHCF) is a set of five herbs comprising 103 compounds belonging to the alkaloid, triterpenoid, and flavonoid families, and were reported to reduce UC. XHCF attenuated DAI scores, colon shortening, inflammatory cell infiltration, repaired tissue structure, and inhibited the phosphorylation of ERK. XHCF also reduced IL-6 and IL-1β expression, M1 polarization, and M2 macrophages number. XHCF inhibited glycolysis, and M1 macrophage polarization promoted adenosine 5' monophosphate-activated protein kinase (AMPK) phosphorylation and regulated ERK phosphorylation [73].

A comparative study by Kang et al. [74] reported the anti-inflammatory effect of *Glycyrrhizae radix* (GR) and *Glycyrrhiza* variety (WG), whose major components are glycyrrhizic acid and liquiritigenin, in DSS-induced UC. GR and WG reduced body weight loss, DAI scores, colon length shortening, IL-6 and TNF-α serum levels, PGE2 levels, mucosal thickness, and tissue damage, and increased the proportion of operational taxonomic units [74]. The effect of *Garcinia mangostana* L. (Clusiaceae) (GM) extract and its bioactive constituent α-mangostin was reported in a mouse model of UC [75]. GM reduced DAI scores, colon shortening, spleen and kidney enlargement, colonic damage, inflammatory cell infiltration, MPO activity, aspartate and alanine aminotransferase, and ALP levels. It also protected tissue integrity and suppressed oxidative response. Additionally, GM reduced TNF-α, suppressed TLR-2, MCP-1, ICAM-1 and vascular cell adhesion protein 1 (VCAM-1) adhesion molecules [75].

Pengkumsri et al. [76] reported the effectiveness of black rice bran (BRB) extract and yeast β-glucan (YBG), alone or combined, in a DSS-induced colitis animal model. The BRB extract contained a substantial quantity of phenolic acids and anthocyanins, while the YBG extract contained 93% of β-glucan. Both the extracts reduced body weight loss, oxidative stress, IL-6, IL-17 and IFN-γ levels. They also increased IL-10 and TGF-β levels and improved the colitis damage. Mango extract containing monogalloyl glucoside, gallic acid, p-hydroxybenzoic acid glycoside, dihydrophaseic acid, and gallotanins ameliorated intestinal inflammation. The extract reduced NF-κB expression, regulated the mTOR pathway, p70S6K1 and ribosomal protein S6 (RBS6) phosphorylation, suppressed phosphoinositide 3-kinase (PI3K) and hypoxia-inducible factor 1 α (HIF1α) proteins, and upregulated miR-126. The extract also reduced the inflammation score, TNF-α, IL-6, IL-1β, iNOS, COX-2, PI3K, mTOR, p70S6 K and HIF1α expressions [77].

The flavonoids-rich extract from *Zanthoxylum bungeanum* Maxim. (Rutaceae) pericarp reduced body weight loss, colon length shortening, and pathological damage to the colon induced by DSS. It also decreased the production of TNF-α, IL-1β, and IL-12 through regulating TLR4-related pathways in colitis [78]. A nanoparticle derived from edible ginger (GDNPs 2) effectively prevented IBD and colon carcinogenesis. The nanoparticle treatment reduced lipocalin-2 (a biomarker for inflammation) levels, infiltration of inflammatory cells, and MPO activity, and increased E-cadherin, an important biomarker in intestinal homeostasis. It also prevented any increase in the pro-inflammatory cytokines TNF-α, IL-1β and IL-6, upregulated IL-10 and IL-22, and reduced apoptotic epithelial cells [56].

Prunus mume Siebold & Zucc. (Rosaceae) juice fermented with *Lactobacillus* strains contains organic and free amino acids, which protect against colitis in mice. It reduced the shortening of colon length, MDA levels, the pro-inflammatory serum cytokines TNF-α, IFN-γ, IL-6, IL-1β and IL-12, colonic tissue TNF-α, IL-12 and IL-17, and the number of apoptotic cells in intestinal tissue. Additionally, the fermented juice increased crypt restoration, and decreased epithelial erosion [79]. A study on the total methanolic extract of *Jasminum grandiflorum* L. subsp. (Oleaceae) reported that the *J. grandiflorum* improved the macro- and micro-scopical ulcer index and histological scores in colon tissues. Chemo profiles of the plant revealed the presence of copious amounts of secoiridoids, terpenoids, flavonoids, and tannins. The extract downregulated the intestinal secretions of the pro-inflammatory cytokines IFNγ, TNF-α, IL-6, IL-1, and MPO in the colonic mucosa. In addition, the extract retained the tight junctions of intestinal epithelial cells, balancing the amount of occludin and CLDN-5. Additionally, the extract reduced expression of NF-κBp65, TNF-α, and caspase-3 [80].

Atractylodes macrocephala Koidz (Asteraceae) and *Taraxacum herba* Weber ex Wigg (Asteraceae) extracts, which contain triterpenoids, polyacetylenes, coumarins, steroids, and polysaccharides, reduced the inflammatory mediators via inactivating extracellular signal-regulated kinase and suppressing NF-κB, and STAT3 pathways in DSS-induced mice colitis. The extracts also exhibited anti-inflammatory effects through preventing macrophage infiltrations of T-lymphocyte, and HO-1 induction [81]. A study on the ethanolic extract of *Aster glehni* Fr. Schm (Asteraceae), showed that it contains an abundant amount of phenolic and flavonoid constituents, which reduces DSS-induced DAI scores, diarrhea, severe bleeding, and immune cell infiltrations. It also protected against spleen expansion, and colon shortening, and prevented intestinal injury caused by increased muscle layer thickness. Additionally, the extract downregulated the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6, as well as the protein expressions of COX-2 and iNOS. NF-κB activation, the nuclear translocation of the p65 NF-κB subunit, and the phosphorylation/degradation of NF-κB inhibitor α were also inhibited by the extract [82]. NF-κB signaling is the most important pathway for the onset and progression of IBD. The progression of IBD occurs with the overproduction of inflammatory cytokines in the intestine, which is stimulated by NF-κB-mediated signaling factors. Many natural substances in this study focus on regulating NF-κB signaling mediated inflammation as a way to treat IBD (Fig. 4). Numerous studies have proven that IBD patients have a higher chance of developing colorectal cancer, which is associated with high levels of inflammatory cytokines in the digestive system [8]. *Curcuma xanthorrhiza* Roxb. (Zingiberaceae) rhizome containing high quantities of bioactive compounds, such as camphene, curcumene, and monoterpene, reduced MPO activity, colon shortening, histological alterations, and DAI scores. The extract also reduced the acute-phase proteins, pro-inflammatory cytokines, matrix metalloproteinase, and its inhibitor. Additionally, it decreased COX-2 and serum S100 calcium-binding protein as well as blocked NF-κB [83].

Phytochemical extracts from muscadine grapes or wine, muscadine grape phytochemicals (MGP), or muscadine wine phytochemicals (MWP) were effective against DSS-induced colitis in mice. Phenolic-rich MGP and MWP reduced DAI, conserved intestinal length, and prevented body weight loss. They also downregulated MPO activity, IL-1β, IL-6, and TNF-α. They dose-dependently inhibited IκB phosphorylation and degradation, resulting in down-regulation of the NF-κB signaling pathway. MWP or MGP reduced the generation of pro-inflammatory cytokines by modulating the NF-κB pathway in UC mice [84].

A study with dietary sugar cane extract comprising phenolic compounds and sterols on the tight junctions in the colon showed that it was effective against inflammation, oxidative stress, splenic and colonic histological abnormalities induced by DSS. It also reduced p65 nuclear aggregation, Nrf2 nuclear accumulation, activated NF-κB p65, and inhibited Nrf2 [85].

Ethanolic extract of *Persea americana* Mill. (Lauraceae) containing copious amounts of phytochemicals, such as saponins, flavonoids, and alkaloids, was effective against clinical symptoms and histological traits induced by DSS. It also downregulated the expression of inducible iNOS, COX-2, and pro-inflammatory cytokines, such as IL-6, IL-1β, and TNF-α in colonic tissues. Additionally, the extract controlled DSS colitis by inhibiting the NF-κB and STAT3 signaling pathway, proving it a promising treatment against IBD illnesses [86]. Akanda et al. [87] showed the inhibitory effects of ethanol extract of *Veronica polita* Fr. (Plantaginaceae) on experimental colitis induced by DSS in mice. The extract contained numerous phenolic and flavonoid components, reduced the DAI score, decreased the degree of histological damage in the colon and spleen, and reduced body weight loss, bloody stool, and the shortening of the colon in DSS-induced mice. Additionally, *V. polita* extract reduced the level of NO, MDA and the expressions of TNF-α, IL-1β, IL-6, iNOS, and COX-2 in the colon tissue. Also, *V. polita* extract with its efficient anti-inflammatory role inhibited the JAK2/STAT3 and NF-κB signaling pathways in colonic inflammation [87].

Graviola leaves were studied for their preventive role against AA-induced UC [88]. The major secondary metabolites identified in the plant include acetogenins, alkaloids and polyphenols with a variety of therapeutic properties. Graviola reduced intestinal damage, oxidative stress, decreased NO and MDA levels, and increased MPO and GSH activity. It upregulated the expression of the anti-apoptotic protein B-cell lymphoma (Bcl) 2 and downregulated the expression of Bcl-2 associated X protein (Bax) and caspase-3. Graviola also decreased AA-induced apoptosis. Furthermore, it downregulated wingless related integration site (Wnt) 1 messenger RNA (mRNA) levels and concurrent upregulation of smoothened and glioma-associated oncogene homologue 1.

Bryophyllum pinnatum (Lam.) Oken. (Crassulaceae) leaf extract, which contains active constituents belonging to the polyphenols, tannins and steroidal glycosides was tested for their anti-inflammatory and antioxidative properties. The extract decreased macroscopic and microscopic damage and displayed anti-inflammatory and chemopreventive properties. It downregulated the NF-κB-p65, decreasing pro-inflammatory and oxidative mediators, chemokines, and cell adhesion molecules. The extract also decreased MDA and MPO activity, increasing GSH levels in the colonic tissue, thereby improving intestinal damage and leukocyte infiltration [89].

Aqueous and methanol extracts from stem and bark of *Alstonia boonei* De Wild. (Apocynaceae) were reported for their antioxidant and anti-inflammatory properties in DSS-induced intestinal colitis. The phytochemical analysis of the plant showed substantial alkaloid, tannin, and steroid contents. Both extracts reduced inflammation and long-term colon damage in rats. The extracts successfully decreased the levels of NO and MDA, and increased the levels of SOD, CAT, and GSH. These results showed the anti-colitis effects of the methanol and aqueous extracts of *A. boonei* stem bark [90]. In DSS-induced chronic colitis in C57BL/6 mice, *Turbinaria ornata* Turner (Sargassaceae) reduced intestinal inflammation by increasing the anti-inflammatory cytokine IL-10, which directly suppresses macrophages and the production of pro-inflammatory cytokines, resulting in diminished colitis [57].

The study by da Silva et al. [91] showed that *Ipomoea asarifolia* (Desr.) Roem. & Schult (Convolvulaceae) aqueous extract containing phenols and flavonoids could prevent colitis in rats induced by DNBS. *I. asarifolia* extract prevented intestinal inflammation with improved DAI and reduced macroscopic damage. The extracts also improved oxidative stress, decreased MPO activity, downregulated the expression of JNK1, NF-κβ p65, STAT3, TNF-α, IL-1β, and upregulated IL-10, MDA, and GSH levels in colonic tissue. These results described above show that natural remedies significantly lower the risk of developing IBD complications by boosting anti-inflammatory properties, increasing antioxidant activity, and strengthening gut health (Fig. 5).

6.5. Effect of isolated phytochemicals on interleukins and other inflammatory modulators in IBD

Biologically active phytochemicals from NPs have been the target of great interest in the search for molecules to develop new drugs for various diseases, including IBD, due to their molecular complexity [21]. Sinapic acid was effective in ameliorating UC in a DSS-induced

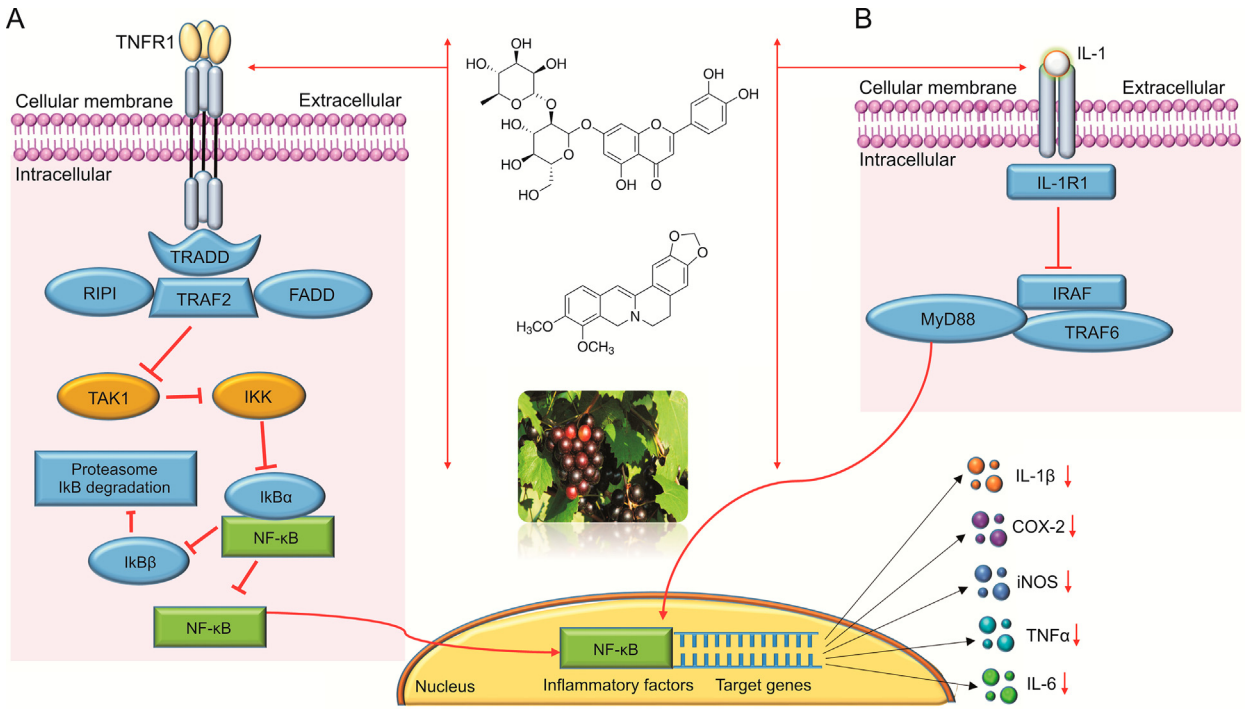

Fig. 4. The nuclear factor kappa B (NF-κB) pathway is inhibited or suppressed using natural substances and phytochemicals, playing a significant role in initiating inflammatory bowel disease (IBD). (A) Ligation of tumor necrosis factor receptor-1 (TNFR1) leads to tumor necrosis factor receptor type 1-associated death domain protein (TRADD) recruitment, interacting with TNFR-associated factor 2 (TRAF2) and Fas associated via death domain (FADD). Transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1) phosphorylates and activates IkappaB kinase (IKK), while nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor, alpha (IkBα) allows NF-κB dimers to translocate to the nucleus and activate inflammatory mediators. (B) Interleukin 1 receptor, type I (IL-1RI) mediates signal transduction through myeloid differentiation primary response 88 (MyD88) and interacts with IRAF, and TNF receptor-associated factor 6 (TRAF6). This phosphorylation allows interleukin (IL-1) dimers to translocate to the nucleus and drive the target gene's transcription (inhibition/suppression).

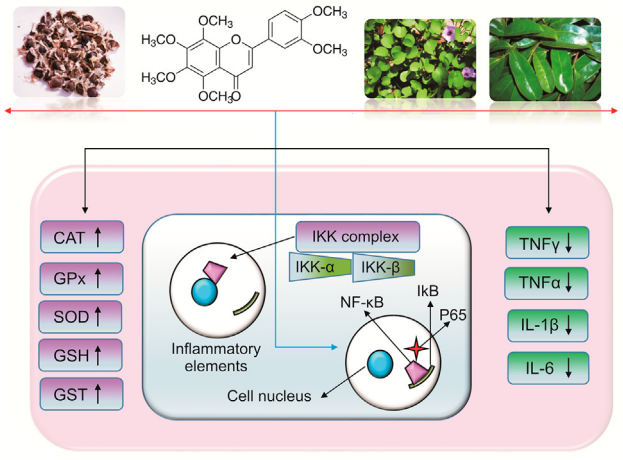

Fig. 5. Natural substances inhibit oxidative stress: Egyptian propolis, nobiletin and *Moringa oleifera* seeds significantly inhibited inflammatory mediators by down-regulating nuclear factor kappa B (NF-κB)-mediated signaling molecules and inflammatory cytokines. They also improved the antioxidant markers such as glutathione (GSH), glutathione s-transferase (GST), superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT). IKK: IkappaB kinase; IL: interleukin; TNF: tumor necrosis factor; INF: interferon.

mice model. The treatment with sinapic acid reduced body weight loss, diarrhea and gross bleeding in colitis mice, while at the same time reducing colon length shortening and conserving colon weight. The treatment also decreased MDA levels, MPO accumulation, inflammation scores, and oxidative stress by reducing SOD, glutathione peroxidase (GPx), and CAT antioxidant enzymes. Sinapic acid reduced pro-inflammatory cytokines levels, LPS, and fluorescein isothiocyanate-dextran 40, and increased anti-inflammatory cytokines, CLDN-1, occludin, ZO-1, nod-like receptor family pyrin domain containing 3 (NLRP3), apoptosis-associated speck-like protein containing a caspase recruitment domain, IL-1β and caspase-1. These findings illustrate the beneficial activity of sinapic acid on UC [92].

Tambuwala et al. [93] assessed the effect of caffeic acid phenethyl ester and piceatannol compounds within an albumin nanoencapsulation in a colitis mice model. The treatment with caffeic acid phenethyl ester and piceatannol ameliorated body weight loss, improved DAI, and alleviated inflammatory symptoms. The treatment also prevented shortening of colon length, colon weight loss, inflammatory neutrophils cells infiltration, and cryptic damage, in addition to reducing MPO expression, INF-γ, IL-6 and TNF-α levels, and HIF1α and p65. The compounds nanoencapsulation improved their activity in colitis [93].

The compounds 6, 8, and 10-gingerol were evaluated against DSS-induced acute UC in rats and were found to attenuate colitis symptoms and reduce body weight loss, DAI scores, oxidative stress via a reduction in MPO and MDA levels, and restore SOD activity. Additionally, they decreased serum pro-inflammatory cytokines (TNF-α and IL-1β), and mucosa inflammation and damage [94]. Another study evaluated quercetin activity in intestinal oxidative damage. Quercetin treatment effectively reduced body weight loss, mucosal erosions, lamina propria inflammatory cell infiltration, and shortening of colon length. It also reduced the increased intestinal permeability and oxidative stress, evidenced by increased GSH levels, and SOD and CAT activity. In vitro, quercetin protected Caco2 cells from H_2O_2 damage, modulated intracellular GSH, and had a protective effect on ROS generation [95].

A phytocannabinoid cannabidivarin effectively reduced colon weight and length, MPO activity, colon damage, mucosal ulcerations, cell inflammatory infiltration, and also ameliorated intestinal permeability. The compound treatment down-regulated the pro-inflammatory cytokines IL-1β, IL-6, and MCP-1. A reduced microbiota profile alteration was also observed in the phytocannabinoid treated group, in addition to modulating transient receptor potential ankyrin type-1 [96].

A 75 kDa glycoprotein isolated from *Cudrania tricuspidata* (Carrière) Bureau ex Lavallée (Moraceae) fruit, with a carbohydrate content of 72.5% and a protein content of 27.5%, induced human colonic epithelial cell proliferation and reduced colitis in a mouse model. The glycoprotein had an important role in cell proliferation, inducing protein kinase C and JNK phosphorylation. These two proteins activated NF-κB, which induced the expression of cell cycle proteins, cyclin D1, cyclin E, and cyclin-dependent kinase (CDK) 2/4, leading to cell proliferation. Glycoprotein also modulated colitis, reduced the DAI score and inhibited colonic shortening. In addition, histological analysis showed a reduction in inflammation and damage to the animals' crypts, with the recovery of the intestinal structure [97].

Luo et al. [98] evaluated the effect of a menthol supplement diet (MSD) on the gut microbiome and against colitis-associated colon cancer induced in mice. The MSD increased colon length and decreased liver and spleen weights, inhibited intestinal inflammation, reduced the number of small adenomas, alleviated pathological damage, and reduced the expression of proliferative proteins, such as β-catenin and Ki67. It also reduced the expression of pro-inflammatory cytokines (IL-6 and TNF-α) and MPO, increased the anti-inflammatory cytokine IL-10, and reduced leukocytes, neutrophils, and myeloid-derived suppressor cells in the spleens of colitis-associated colon cancer mice, as well as induced the development of butyrate-producing bacteria [98].

Cinnamaldehyde is a cinnamon bioactive tested for its ability to improve AA-induced colitis in mice. It reduced tissue damage and the size of ulcers. Additionally, cinnamaldehyde inhibited inflammation, mucosal injury, edema, hemorrhage and ameliorated epithelization. It also reduced MPO and granulocytic cell activity, TNF-α, and suppressed the mRNA level of TLR-4, an important receptor involved in colonic inflammation [99].

The effect of α-mangostin against UC in mice was extensively studied. It reduced DAI scores, shortening of colon length, kidney enlargement, tissue damage, cell infiltration, and MPO activity. It also decreased ALP, aspartate aminotransferase levels, TNF-α, TLR-2, MCP-1, VCAM-1, and ICAM-1. It reduced oxidative stress and protected mucosal integrity [75]. The ability of a complex of nine plant sterol ester compounds: brassicasterol, campesterol, campestanol, stigmasterol, β-sitosterol, β-sitostanol, D5-avenasterol, D7-stigmastenol, and D7-avenasterol, to inhibit colon carcinogenesis was investigated by Sadek et al. [100]. The complex reduced liver and kidney inflammation, liver necrosis, kidney hemorrhagic levels, fatty degeneration, colon weights, and COX-2 expression, and increased caspase-3, -8 and -9 expression. Overall, the complex reduced inflammation and induced cell apoptosis [100].

Gu et al. [101] evaluated the effect of chitosan and chitooligosaccharides on inflammation in the intestine of turbots. Both compounds regulated body weight loss, feed efficiency, growth rate and condition, the height of mucosal folds, lysozyme and acid phosphatase activities, IgM concentration, and diversity in the intestine mucosa. Additionally, it decreased cell infiltration, IL-1β, IL-8, activation protein 1 (AP-1), NF-κB, TNF-α, p38, JNK, ERK expressions and lipid peroxidation [101].

A study conducted by Raj et al. [102] assessed the effect of nerolidol (NED) on DSS-induced colonic inflammation. NED reduced the DAI and prevented the shortening of the colon length. NED also decreased MPO levels, chemokine (C–X–C motif) ligand 2 (CXCL2) and chemokine (C-C motif) ligands 2 (CCL2) mRNA expression, IL-1β, IL-6, TNF-α, COX-2, and iNOS, and promoted Nrf2 translocation. NED also increased the activity of SOD, CAT, HO-1 and SOD3 mRNA levels. In addition, NED exerted antioxidant and anti-inflammatory activity on colon inflammation [102].

Rehman and Rather [103] reported the oxidative stress inhibitory effect of myricetin, a flavonoid found in fruits, teas, and plants. Myricetin restored levels of antioxidant enzymes, improved lipid peroxidation, and increased the activity of xanthine oxidase and phase II detoxifying enzyme. Myricetin also reduced NF-κB, Nrf2, IL-6 and TNF-α and controlled the disintegration of goblet cells in rats [103]. Guo et al. [104] evaluated the anti-inflammatory effects of eriocitrin on DSS-induced colitis in mice. Eriocitrin ameliorated all deleterious effects caused by DSS, such as colon shortening, body weight loss, histopathological lesion, IL-6, IL-1β and TNF-α expression, and accumulation of inflammatory cells in the colon [104]. Quercetin (QCT) prevented minor intestine damage and increased intestinal recovery in mucositis in rats. Sukhotnik et al. [105] reported that QCT reduced the intestinal lesion score, and regulated the weight of the intestine, mucosa of jejunum and ileum, the protein content of the ileum, and the height of its villi. QCT also increased the depth of the jejunum and ileum crypts and cell proliferation, preventing intestinal damage in mucositis.

A study conducted by Yu et al. [106] reported that GB1a, a natural molecule that reduces colonic inflammation, reversed body weight loss and DAI scores in UC mice. GB1a increased the intestinal epithelium by regulating the production of tight junction proteins (ZO-1). Additionally, GB1a downregulated NF-κB and activated Nrf2 signaling to reduce inflammation, oxidative stress, and colonic epithelial mucosa permeability in UC mice [106]. Another study with dihydroberberine reduced the UC symptoms, and DAI scores and the pathological damage caused by DSS. Dihydroberberine also improved the intestinal barrier through increased concentrations of mucins and tight junction proteins. Moreover, it blocked the TLR4/MyD88/NF-κB signaling pathways. Overall, dihydroberberine decreased the pro-inflammatory cytokines in colitis [28].

Nerolidol, a natural compound found in plant essential oils alleviated body weight loss, enhanced histology, prevented the development of MDA, restored antioxidants, and decreased MPO activity in an AA-induced colitis model in Wistar rats. Nerolidol reduced levels of pro-inflammatory cytokines, decreasing inflammation, as well as reducing oxidative stress and conserving the colon's histological tissues. These beneficial effects of nerolidol were associated with the inhibition of inflammatory mediators and signaling pathways, such as the lectin-type oxidized low-density lipoprotein receptor (LOX-1), IL-1β, TLR4/NF-κB signaling, and the AMPK/Nrf2/HO-1 pathway [1].

A crude polysaccharide from *Cynanchum wilfordii* Hemsley (Asclepiadaceae) (HMFO) decreased pro-inflammatory cytokine production and improved colitis' pathological aspects. HMFO restored the histological damage caused by DSS like aberrant crypts, crypt loss, and inflammatory cell infiltration. Additionally, HMFO suppressed several inflammatory cytokines and enzymes, including PGE2, NO, TNF-α, IL-6, iNOS, and COX-2. It also reduced the expression of iNOS, COX-2, NF-κB, MAPK, and phosphorylated NF-κB p65, and prevented NF-κB activation [107].

A study by Liu et al. [108] reported that three flavonoids, hyperoside, lonicerin and luteolin, had anti-oxidative and anti-inflammatory properties against TNBS-induced UC. The oxidative and pro-inflammatory markers SOD, MPO, MDA, PGE2, TNF-α, IL-β, and CRP were reduced by the flavonoids, and also downregulated the NF-κB signaling pathway, proving its anti-UC activity [108]. Crude polysaccharides from *Physalis pubescens* L. (Solanaceae) reduced the expression of ICAM-1 and MCP-1 on DSS-induced

colitis. The extract also protected the colon mucosal layer, maintained the intestinal barrier integrity, reduced oxidative damage, and decreased neutrophil infiltration. It also reduced intestinal damage, and downregulated the expression of TNF-α, iNOS and COX-2, modulating the NF-κB/iNOS-COX-2 signal transduction pathway [109].

Licorice flavonoids are strong anti-inflammatory NPs that decrease the production of inflammatory cytokines via activation of NF-κB and the phosphorylation of JAK2/STAT3. Licorice also prevented colitis-associated carcinogenesis induced by azoxymethane (AOM)/DSS through the p53 and NF-κB/IL-6/JAK2/STAT3 pathways [110]. Feruloylated oligosaccharides lowered the production and proportion of Th17-specific cytokines and cells. In contrast, the oligosaccharides boosted the production and proportion of Treg-specific cytokines and cells in the colons of DSS-challenged mice. By maintaining the immunologic balance of the Th17 and Treg subsets, feruloylated oligosaccharides prevented colitis. Additionally, it downregulated the release of IL-23, and IL-6 and upregulated TGF-β1 in dendritic cells, which restored the balance between Th17 and Treg cells in the immune system. By rebuilding the immunological balance between Th17 and Treg cells, feruloylated oligosaccharides proved its substantial immunomodulatory benefits against mice colitis [111]. These results indicate the ability of NPs to effectively restore the overall gut Th17/Treg cell immune balance, and be used as beneficial dietary supplements in functional foods to treat IBD and associated complications (Fig. 6).

Using a translatable mouse model of IBD, Riemschneider et al. [112] examined the therapeutic efficacy of QCT and indol-3-carbinol, two plant-derived ligands of the aryl hydrocarbon receptor (AhR). QCT and indol-3-carbinol decreased GI inflammation evidenced by the lower levels of neutrophils and macrophages. It also alleviated clinical symptoms in DSS colitis and repaired the loss of epithelial integrity by inducing tight-junction proteins. Additionally, QCT and indol-3-carbinol therapy greatly increased the Treg cells while significantly decreasing the Th17 cells [112]. Nobiletin and its primary metabolites were studied for their anti-inflammatory and anticancer effects on lipopolysaccharide-induced colonic tissues. Nobiletin lowered the levels of iNOS, HO-1, nicotinamide adenine dinucleotide (NADH), and quinone oxidoreductase 1, and upregulated the Nrf2 signaling pathway. Nobiletin upregulated Nrf2-dependent enzymes, lowered the level of iNOS, increased antioxidant enzymes, and prevented cell cycle progression [113].

6.6. Effects of plant substances and natural molecules on colitis symptoms

The present study's findings demonstrate the importance of segregating and collecting evidence on the therapeutic and preventative effects of administering naturally derived substances in experimental animal models of IBD. Most studies revealed that interleukins and their associated signaling pathways can be regulated by natural agents that are high in polyphenols, effectively decreasing intestinal inflammation and colitis symptoms (Table 1). Plants with high levels of polyphenols are advantageous because of their innate capacity to neutralize free radicals, trigger anti-inflammatory reactions, uphold homeostatic control of the gut microbiota, and activate intestinal Treg cells [43]. Results from studies suggest that the beneficial effects of purple-fleshed potatoes, chestnut shell extract, graviola leaf extract, rosemary extract, polyphenolic-rich mango extract, ginger, pennyroyal phenolic extract, muscadine grapes, sugar cane extract, pomegranate juice, polyphenol extract from cranberry fruits, green and dark tea extract, polyphenol-rich extract of *O. gratissimum,* and Egyptian propolis methanol extract, which are rich in polyphenols and antioxidants, reduced colitis symptoms by decreasing the inflammatory mediators, reflecting in improved DAI scores, in addition to improving body weight gain and colon length.

The most optimistic findings are shown in Table 2, in which nerolidol, quercetin, 6- 8- and 10-gingerol, nobiletin, licorice flavonoids, hyperoside, lonicerin, luteolin, nerolidol, myricetin, and eriocitrin, which are found in several edible plants like vegetables, fruits, whole grains, legumes, nuts, and seeds, were shown to possess multiple pharmacological effects. The results of preclinical studies showed that these compounds are effective in preventing colitis symptoms in rats and mice. It was also shown that these natural molecules predominantly reduced the infiltration of inflammatory cells into the mucosal layer of the intestine and shortening of the colon. Studies have also shown the ability of natural molecules to halt weight loss and reduce colonic inflammation by scavenging free radicals through increasing GSH, SOD and CAT activity.

6.7. Summary of important molecular pathways involved in IBD

Many molecular pathways are involved in IBD, but the STAT3 pathway is the most significant pathway in respect of the pathophysiology of IBD. It is extensively expressed in many cell types including T cells, macrophages, and epithelial cells [114]. The STAT3 pathway is typically activated by IL-6, causing chronic inflammation. In a recent study, STAT3 activation was observed in many IBD patients. This intensification in STAT3 during chronic inflammation was strongly connected with the severity of colitis. In addition, Th17 differentiation and its activation are directly associated with IBD. STAT3 produces several pro-inflammatory cytokines including, TNF-α, and IL-6 [115]. For the activation of the STAT3 pathway, phosphorylation at tyrosine residue (Y705) is essential, making it possible for STAT3 to form dimers. The activated STAT3 dimer promotes transcription of the target genes and moves into the nucleus. In cell line models of IBD, STAT1 was found to be more phosphorylated [116]. Thus, the JAK2/STAT3 pathway has proved to be a key signaling route linked to the development of IBD and colitis-associated cancer [117].

An important aspect in determining inflammation is the ratio of Treg cells to pro-inflammatory Th17, which is regulated by the transcription factors retinoic acid related orphan receptor gamma t (RORγt) and fork head box P3 (FoxP3) [118]. In numerous organs, the balance between Th17 and Treg cells is controlled by AhR activation, which controls homeostasis vs inflammatory processes [118]. In mice with DSS-induced colitis, the proportion of Th17 cells and/or innate lymphoid cells 3 (ILC3) was higher, whereas the proportion of Treg cells was lower [112]. This imbalance between Th17 and Treg cells is the reason for the development and spread of IBD. Restoring the equilibrium between the Th17 and Treg subsets regulates the immune systems that maintain colonic immunological homeostasis. Targeting this imbalance could be crucial to treating IBD [119].

Furthermore, colonic inflammation is linked to the production of neutrophils and phagocytes and the induction of oxidative stress; this could be the pathophysiology behind IBD [120]. Recent research has shown that crucial intracellular processes such as oxidative stress, epithelial barrier disruption, accelerated epithelial cell apoptosis, and inhibition of inflammatory and immune cell apoptosis, are strongly linked to the immunological anomaly triggered by UC [121]. Oxidative stress and inflammatory mediators damage the colonic crypts resulting in nuclear β-catenin accumulation and activation of lymphoid enhancer-binding factor 1 (LEF1)/T-cell factor (TCF) target genes like survivin and cyclin D1

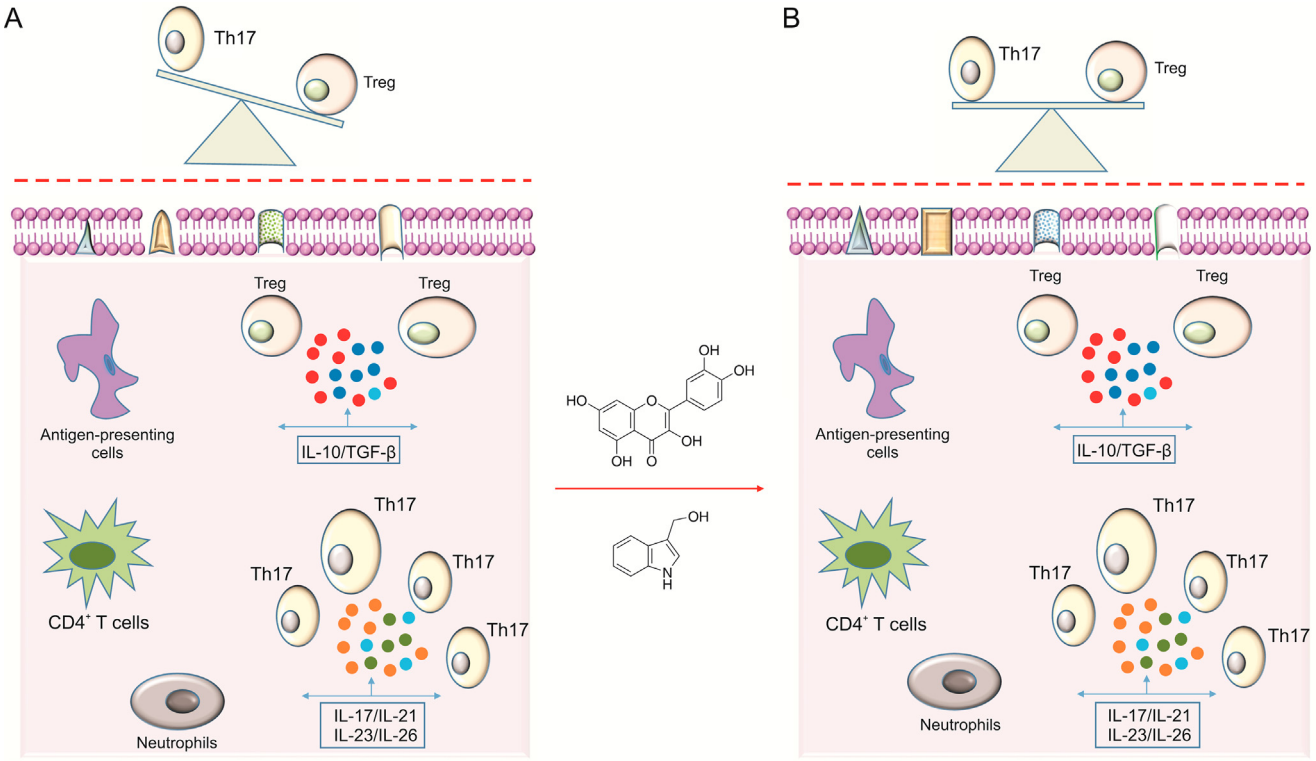

Fig. 6. Natural molecules like quercetin and indol-3-carbinol maintain T helper (Th)17/regulatory T cells (Tregs) balance, restoring immune balance in inflammatory bowel disease (IBD) condition by targeting key immunological markers and restoring Th17/Treg cell balance. IL:interleukin; TGF: transforming growth factor; $CD4^+$: cluster of differentation.

[122]. The activation of survivin and cyclin D1 results in colonic inflammatory damage, apoptosis and finally causes ulcer development [123]. Immune cells, like macrophages, express large levels of NOS in the iNOS isoform upon activation of NF-κB p65 in response to a variety of stimuli, including TNF-α, INF-γ, IL-6, IL-1β, as well as bacterial and viral components. The higher amount of iNOS and NO generation can cause severe tissue damage and exacerbated inflammation, as is seen in IBD patients [124,125]. In animal models of experimental colitis and human IBD, the intestinal inflammatory process is closely linked to the development of oxidative stress, which lowers cellular antioxidant capacity. Free radicals produced in excess can interact with the fatty acids in cell membranes to cause lipid peroxidation, harming the intestinal lining [126].

Inflammatory mediators such as TNF-α, IL-1β, and iNOS are involved in the UC pathogenesis regulated by NF-κB signaling [127,128]. The growth of colorectal tumors is linked to chronic inflammation targeting NF-κB, which is interrelated with the pro-survival signaling mediators survivin, X-linked inhibitor of apoptosis protein (XIAP), and B-cell lymphoma 2 (Bcl-2) family proteins [129]. Thus, targeting NF-κB inhibitors could be a possible cutting-edge therapeutic approach for IBD management.

7. Conclusion

The use of NPs derived from plant roots, stems, and leaves has grown significantly in modern medicine, including in biopharmaceuticals [24]. In many cases, NPs have become the preferred choice, even during the initial stages of molecular targeted therapy, because of their abilities in respect of immune regulation and anti-inflammation. This review shows that NPs can exert a significant influence on the etiopathogenesis of IBD. There is mounting evidence that the damage to colonic tissue caused by IBD is likely the result of critical intracellular processes such as oxidative stress, epithelial barrier breakdown, increased epithelial cell apoptosis, and the activation of inflammatory and immune cell apoptosis. Using plant extracts and their natural components significantly reduced the damage to colon tissue and prevented weight loss. Furthermore, NPs demonstrated an ability to reduce intestinal inflammation through regulation of the levels of pro-inflammatory cytokine levels such as TNF-α, IL-1β, IL-6, and IL-17, as well as the modulation of the JNK1, NF-κβ/p65, and STAT3 signaling pathways. Taken together, the results of the studies included in this review showed that NPs have the ability to reduce oxidative stress and enhance antioxidant enzyme activity, thereby reducing IBD severity. In conclusion, this systematic review presents a range of important preclinical evidence demonstrating that NPs and their molecules can reduce the severity of IBD by preventing or modulating the inflammatory response associated with IBD, especially in respect of UC. Therefore, further studies, including clinical trials, should be undertaken to further explore the therapeutic properties of these NPs in relation to the treatment of IBD.

CRediT author statement

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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