

World Journal of *Gastroenterology*

World J Gastroenterol 2020 June 28; 26(24): 3318-3516



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ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Dr. Ji is a Distinguished Professor in Shanghai University of Traditional Chinese medicine, Shanghai, China. Having received his Bachelor degree from Yangzhou College of medicine in 1991, Dr. Ji undertook his postgraduate training first at Hubei College of Traditional Chinese medicine, received his Master degree in 1994, and then at Shanghai University of Traditional Chinese medicine, received his PhD in 1997. He became Chief Physician in the Gastroenterology Division, Longhua Hospital affiliated to Shanghai University of Traditional Chinese medicine since 2004. His ongoing research interests are applying Evidence-based medicine methods to study the effects, and managing the disease-syndrome pattern establishment of integrative medicine on digestive diseases. Currently, he is the President of the Shanghai Association for the Study of the Liver with integrative medicine.

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The WJG is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, and Scopus. The 2019 edition of Journal Citation Report® cites the 2018 impact factor for WJG as 3.411 (5-year impact factor: 3.579), ranking WJG as 35th among 84 journals in gastroenterology and hepatology (quartile in category Q2).

RESPONSIBLE EDITORS FOR THIS ISSUE

Electronic Editor: Yan-Liang Zhang; Production Department Director: Yun-Xiaojuan Wu; Editorial Office Director: Ze-Mao Gong.

NAME OF JOURNAL

World Journal of Gastroenterology

ISSN

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE

October 1, 1995

FREQUENCY

Weekly

EDITORS-IN-CHIEF

Andrzej S Tarnawski, Subrata Ghosh

EDITORIAL BOARD MEMBERS

<http://www.wjgnet.com/1007-9327/editorialboard.htm>

PUBLICATION DATE

June 28, 2020

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

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<https://www.wjgnet.com/bpg/GerInfo/287>

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<https://www.wjgnet.com/bpg/GerInfo/288>

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<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Interventions of natural and synthetic agents in inflammatory bowel disease, modulation of nitric oxide pathways

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Abstract

Inflammatory bowel disease (IBD) refers to a group of disorders characterized by chronic inflammation of the gastrointestinal (GI) tract. The elevated levels of nitric oxide (NO) in serum and affected tissues; mainly synthesized by the inducible nitric oxide synthase (iNOS) enzyme; can exacerbate GI inflammation and is one of the major biomarkers of GI inflammation. Various natural and synthetic agents are able to ameliorate GI inflammation and decrease iNOS expression to the extent comparable with some IBD drugs. Thereby, the purpose of this study was to gather a list of natural or synthetic mediators capable of

Conflict-of-interest statement: The authors have no conflicts of interest to disclose.

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Manuscript source: Invited manuscript

Received: February 24, 2020

Peer-review started: February 24, 2020

First decision: April 22, 2020

Revised: May 9, 2020

Accepted: June 4, 2020

Article in press: June 4, 2020

Published online: June 28, 2020

P-Reviewer: Farhat S, Gazouli M, Vradelis S

S-Editor: Gong ZM

L-Editor: Webster JR

E-Editor: Ma YJ



modulating IBD through the NO pathway. Electronic databases including Google Scholar and PubMed were searched from 1980 to May 2018. We found that polyphenols and particularly flavonoids are able to markedly attenuate NO production and iNOS expression through the nuclear factor κ B (NF- κ B) and JAK/STAT signaling pathways. Prebiotics and probiotics can also alter the GI microbiota and reduce NO expression in IBD models through a broad array of mechanisms. A number of synthetic molecules have been found to suppress NO expression either dependent on the NF- κ B signaling pathway (*i.e.*, dexamethasone, pioglitazone, tropisetron) or independent from this pathway (*i.e.*, nicotine, prednisolone, celecoxib, β -adrenoceptor antagonists). Co-administration of natural and synthetic agents can affect the tissue level of NO and may improve IBD symptoms mainly by modulating the Toll like receptor-4 and NF- κ B signaling pathways.

Key words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Nitric oxide; Nuclear factor- κ B; Natural or synthetic mediators

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Core tip: The present study aimed to investigate the correlation between the level of nitric oxide (NO), and inflammatory bowel disease (IBD). Collected data showed that elevated NO can induce gastrointestinal tract inflammation. Many natural and synthetic agents are able to decrease NO production through different pathways, thereby, improving inflammation and IBD symptoms. This study also determined the pharmacological effects of these agents in suppression of the NO pathway.

Citation: Kamalian A, Sohrabi Asl M, Dolatshahi M, Afshari K, Shamshiri S, Momeni Roudsari N, Momtaz S, Rahimi R, Abdollahi M, Abdolghaffari AH. Interventions of natural and synthetic agents in inflammatory bowel disease, modulation of nitric oxide pathways. *World J Gastroenterol* 2020; 26(24): 3365-3400

URL: <https://www.wjgnet.com/1007-9327/full/v26/i24/3365.htm>

DOI: <https://dx.doi.org/10.3748/wjg.v26.i24.3365>

INTRODUCTION

Inflammatory bowel disease (IBD) is commonly comprised of Crohn's disease (CD) and ulcerative colitis (UC), and is a worldwide health issue, afflicting a continually increasing number of people^[1]. Generally, IBD is characterized by chronic or relapsing inflammation of the gastrointestinal (GI) tract^[2]. CD is associated with the transmural inflammation of potentially any part of the GI tract (mainly the terminal ileum and colon), usually without bleeding and concomitant complications including strictures, abscesses, and fistulas. However, UC only affects the mucosal layer of the colon (especially the rectum) and leads to rectal bleeding^[3]. In spite of apparent differences in histological aspects and clinical manifestations of UC and CD, they share noticeable similarities from a pathophysiological point of view. In this regard, aberrant immune response to the microbial and environmental stimuli precipitated by genetic predispositions is assumed to result in IBD^[4-6]. Notably, many factors involved in IBD converge within the intestinal inflammation, representing inflammatory cells infiltration and accelerating the inflammatory cytokines and nitric oxide (NO) release.

NO AND THE PATHOPHYSIOLOGY OF IBD

NO is an essential inorganic molecule with various physiological and pathological implications. NO is a free radical synthesized from the amino acid L-arginine (L-Arg) in a reaction catalyzed by the nitric oxide synthases (NOS) enzyme group. A number of NOS such as neuronal NOS (nNOS) and endothelial NOS (eNOS), also called constitutive NOS, are minimally expressed within the inflamed sites. However, inducible NOS (iNOS) is highly expressed in inflammatory cells in response to immunogenic stimuli, majorly in association with a different CD4⁺ helper T cell

profile based on the Th2/Th1 paradigm and pro-inflammatory cytokines through the activation of mitogen-activated protein kinases (MAPK) and NF- κ B^[7-9]. Thus, CD was described as a Th1 type immune response promoted by signal transducer and activator of transcription (STAT)-4 and T-bet; which are able to produce interferon gamma (IFN- γ), interleukin (IL)-12, and tumor necrosis factor (TNF)- α . It has been shown that both IL-12 and IL-18 induce a high level of IFN- γ production, leading to reinforcement of the Th1 immune response. In contrast, UC is recognized as a Th2 type immune response prompted by the expression of transcription factor STAT-6 and GATA-3, as well as the secretion of IL-5, IL-4, and IL-13^[9]. Obviously, an adequate amount of this immune response in the intestines is necessary for protection against infections, but excessive production of NO may exert pathologic effects^[9-11].

iNOS is mainly activated through the activator protein-1 (AP-1) assembly; and activation of the extracellular signal-regulated kinase (ERK), leading to the phosphorylation and activation of I κ B- of I κ B-kinase- β (IKK- β) and cytosolic phospholipase A2, and upregulation of arachidonic acid (AA) release. An upsurge of NF- κ B nuclear translocation, activates cyclooxygenase-2 (COX-2) by S-nitrosylation. COX-2 inevitably triggers the excessive production of prostaglandin E2 (PGE 2)^[12].

The primary hypothesis of the involvement of NO in the pathogenesis of IBD was based on the presence of NO and its metabolites in the intestinal lumen and biological fluids (*i.e.*, plasma and urine) in patients with IBD, more predominantly observed in their remission phase and in severe disease^[11,13-15]. Rather than inflammation, many features of IBD are correlated with excessive NO; which can directly act on the endothelium and smooth muscle cells or may affect the epithelium, resulting in edema, vasodilatation, and increased mucosal permeability^[16]. Overproduction of NO also stimulates chloride secretion in the colon, leading to diarrhea; one of the main features of IBD^[17]. NO may play a pivotal role in the pathogenesis of some types of IBD such as toxic megacolon, through regulation of intestinal motility and mucosal blood supply^[18].

As mentioned earlier, iNOS is preliminarily activated by pro-inflammatory cytokines and immunogenic stimuli, acting *via* the JAK/STAT signaling pathways^[9]. Activation of iNOS and irregular production of NO by pro-inflammatory (*i.e.*, TNF- α , IFN- γ , IL-1b, IL-4, IL-5, IL-6, IL-8, IL-12, IL-13, IL-17, IL-18 or IL-23) and inflammatory molecules (*i.e.*, lipopolysaccharide (LPS)^[9,10,19], results in further propagation of inflammatory responses by chemotaxis of neutrophils, natural killer (NK) cells and macrophages. In addition, NO indirectly induces reactive nitric oxygen species (RNOS) production. Then, it might react with superoxide, thus, generating peroxynitrite (OONO \cdot). OONO \cdot is an oxidant for several biological molecules, for example, it can activate the poly (-ADP-ribose) synthetase (PARS) enzyme, leading to depletion of adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NAD) cellular supply, thereby, enhancing the epithelial permeability of the intestine^[15,20,21]. Furthermore, NO can suppress mitochondrial function and DNA synthesis through OONO \cdot production. It also enhances the intracellular release of iron, thus, acting as a cytotoxic agent and perpetuating the mucosal injury and inflammation^[15]. Beyond OONO \cdot production, NO induces RNOS species (*i.e.*, NO $_2$ and NO \cdot) production^[22]. It seems that there is a bidirectional interaction between NO production and inflammation in IBD, each one exacerbating the other^[9]. Molecular pathways involved in IBD progression are shown in **Figure 1**.

Despite accumulating evidence supporting the role of excessive NO in the perpetuation of inflammatory responses, various research groups have shown that NO can exert immunomodulatory effects by inhibiting IL-12 secretion^[23]. Additionally, some studies have shown that iNOS-deficient mice are more susceptible to colitis, as NO can suppress IL-17 secretion^[24,25]. In line with previous findings, it has been shown that induction of iNOS alleviates mucosal injury and improves tissue repair^[25]. In addition, nitrite supplementation and stimulation of NO release alleviated mucosal damage in a dextran sulfate sodium (DSS) model of colitis^[26,27]. The pathophysiological significance of NO in the GI tract and possible efficacy of either natural or synthetic agents on NO have been reviewed by many studies, however, none of them extensively discussed both natural and synthetic interventions. This might allow opportunities for IBD drug development mediated by the NO pathway^[2,28].

In spite of such controversies, suppression of NO-dependent pathological events by natural or synthetic agents was shown to attenuate IBD inflammation and symptoms in animal models (**Figure 2**). This paper reviews the pharmacological interventions of natural and synthetic agents that can affect IBD through the NO pathway.

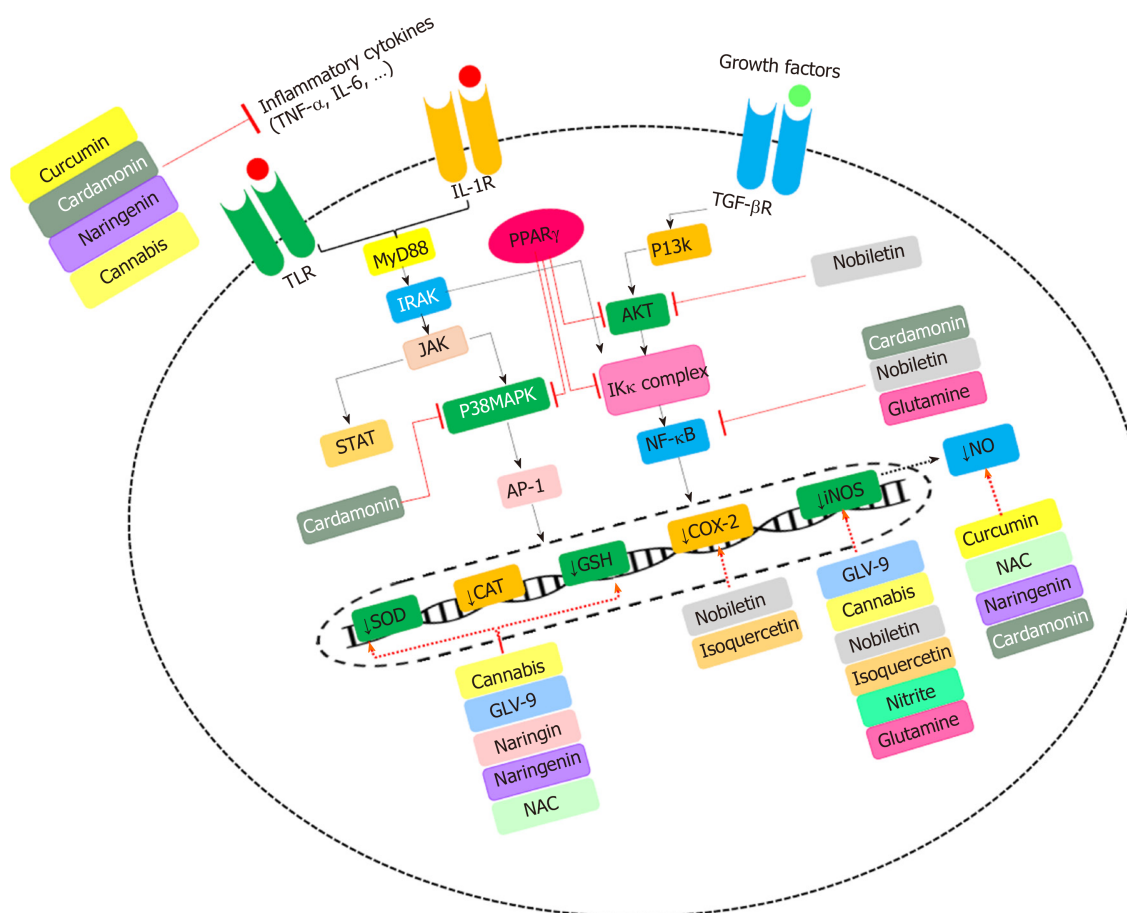


Figure 1 Main cellular mechanism of interventions in inflammatory bowel disease. COX-2: Cyclooxygenase-2; iNOS: Inducible nitric oxide synthase; TNF- α : Tumor necrosis factor alpha; NF- κ B: Nuclear factor kappa-light-chain-enhancer of activated B cells; I κ B: Inhibitor of kappa B; IKK complex: Inhibitor of kappa kinase complex; MyD88: Myeloid differentiation primary response 88; P38MAPK: P38Mitogen-activated protein kinase; GSH: Glutathione; P13k: Phosphatidylinositol 13-kinase; STAT: Signal transducer and activator of transcription proteins; IL-6: Interleukin-6; IL-1: Interleukin-1; PPAR γ : Peroxisome proliferator-activated receptor gamma; TLR: Toll-like receptor; MCP-1: Monocyte chemoattractant protein-1; AP-1: Activator protein 1; IRAK: Interleukin-1 receptor-associated kinase; NAC: N-acetyl cysteine; NO: Nitric oxide; SOD: Superoxide dismutase; CAT: Catalase; TGF β R: Transforming growth factor beta receptor I.

SEARCH METHOD

We searched published literatures on studies that investigated the effects of natural and synthetic agents on IBD through modulation of the NO pathway. We used broad search terms: "Nitric oxide" or "NO" or "Nitric oxide pathways" and "Inflammatory bowel disease" or "IBD". Electronic databases including Google Scholar and PubMed were searched from 1980 to May 2018, and the abstracts were screened for relevancy. The publications that investigated diseases other than IBD, or the interventions except that of the NO pathway, and studies that were not conducted on animal models, or did not include a synthetic or natural agent, were excluded.

PHARMACOLOGICAL INTERVENTIONS AFFECTING IBD THROUGH THE NO PATHWAY

Medicinal plants

The impressive roles of medicinal plants and their isolated chemical constituents (phytochemicals) in IBD management have been confirmed by numerous studies^[29]. Therefore, medicinal plants seem to have a promising future in IBD treatment^[30]. Following sections contain a number of plant species and their active ingredients that are able to inhibit NO, and were shown to have beneficial impacts on IBD (Table 1).

***Lavandula spica* L. or *L. angustifolia* Mill.:** Members of the *Lavandula* genus, Lamiaceae, have been associated with a reduction of chronic inflammation in various settings, including IBD. Interestingly, *in vitro* studies suggested that more than one species of *Lavandula* works through the NO pathway to reduce inflammation in

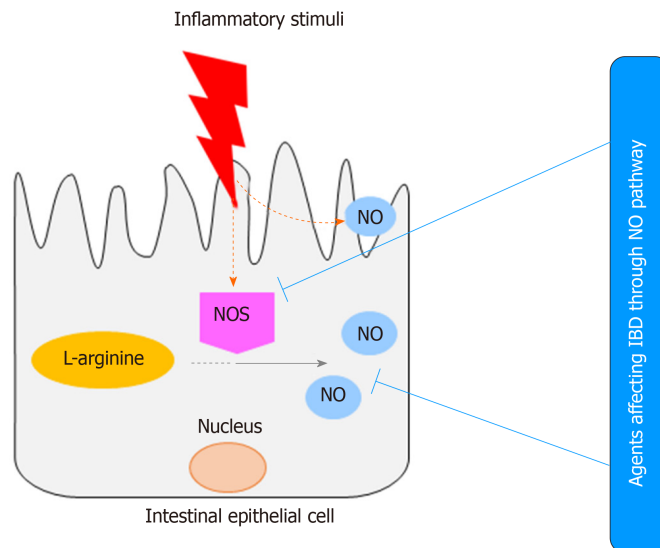


Figure 2 Inhibition of nitric oxide synthase suppresses inflammatory bowel disease. IBD: Inflammatory bowel disease; NOS: Nitric oxide synthase; NO: Nitric oxide.

various cell lines. For instance, the essential oil of *L. eliasii* subsp. *thalictrifolium* specifically reduced iNOS expression in intestinal cell lines, indicating that these subspecies may be more appropriate for IBD settings. As expected, the anti-inflammatory effect of *Lavandula* species was exerted through the NF- κ B signaling pathway^[31,32].

***Cannabis sativa* L.:** The marijuana plant *C. sativa* and its derivatives, Cannabinoids, are known to be a potential therapy for IBD. Cannabigerol and Cannabidiol were found to regulate a set of functions in the body and play a key role in curing IBD, particularly by reducing the production of nitric compounds, with therapeutic effect in colitis mice^[33].

***Olea europaea* L.:** Extracts from olive (*Olea europaea*) leaves are used in different traditional medicines as anti-inflammatory agents. The extract could be a great choice for the treatment of oxidative stress-induced inflammatory conditions, including IBD, mainly due to its antioxidant phenolic content, *i.e.*, Oleuropeoside. This extract inhibited IBD progression, most probably by reducing the production of chemokines and nitrite compounds such as NO^[34].

***Retama monosperma* (L.) Boiss.:** *Retama* spp. is an indigenous component of traditional medicine of Mediterranean regions, and its anti-inflammatory and antioxidant effects have been well accepted. The hypoglycemic effects of this plant have been attributed to the high concentration of Pinitol, a cyclic polyol, present in the aerial parts of *R. monosperma*^[35]. However, the antioxidant activities of this plant have been directly correlated with the titrated concentrations of its flavonoid content^[36]. Oral administration of an aqueous extract of the aerial parts of *R. monosperma* led to a decrease in iNOS expression mediated through the NF- κ B and p38 MAPK signaling pathways^[37].

***Hibiscus rosa-sinensis* L.:** *Hibiscus rosa-sinensis*, also known as rose mallow or China rose, is a species of flowering plant belonging to the family Malvaceae. *H. rosa-sinensis* was shown to have potential therapeutic value in ameliorating experimental colitis in laboratory animals, by inhibiting pro-inflammatory mediators such as NO and TNF- α . The hydroalcoholic extract of the leaves of *H. rosa-sinensis*; containing alkaloids, flavonoids, steroids, and phenols; significantly reduced severity of acetic acid-induced colitis symptoms as assessed by the clinical disease activity score^[38].

***Curcuma longa* L.:** Curcumin is the main constituent of the rhizome of *Curcuma longa*. Inhibition of COX-1, COX-2, TNF- α , iNOS, and NF- κ B, and the potent anti-oxidant and anti-inflammatory effects of curcumin, makes this compound a great pharmacological candidate for patients with IBD^[39].

***Vaccinium corymbosum* L.:** An aqueous extract of highbush blueberry fruit (*Vaccinium*

Table 1 Medicinal plants affecting inflammatory bowel disease *via* modulating nitric oxide pathways

Ref.	Plant	Plant part/ ingredients	Type of animal/cells	Model of IBD	Route of administra- tion	Duration of treatment	Numbers of animals in intervention group and control group	Outcomes
[199]	<i>Terminalia catappa</i>	Stem bark	Rat	2,4,6-trinitrobenzene sulfonic acid (TNBS)	Oral	Two days before colitis induction	<i>n</i> = 6	Disease activity index (DAI) ↓, myeloperoxidase (MPO) ↓, glutathione content ↑, tumor necrosis factor (TNF)-α ↓, interleukin (IL)-6 ↓, IL-23 ↓, cytokine-induced neutrophil chemoattractant-1 ↓, mucin (MUC)-2 ↑, MUC-3 ↑, villin ↑
[200]	<i>Veronica polita</i>	Whole plant	Mice	Dextran sulfate sodium (DSS)	Oral	7 d	<i>n</i> = 10	DAI ↓, malondialdehyde (MDA) ↓, nitric acid (NO) ↓, TNF-α ↓, IL-1β ↓, IL-6 ↓, inducible nitric oxide synthase (iNOS) ↓, cyclooxygenase (COX-2) ↓, nuclear factor (NF)-κB ↓, phosphorylation of Junas kinase/signal transducer and activator of transcription (JAK2/STAT-3) ↓
[32]	<i>Lavandula stoechas</i> / <i>Lavandula dentate</i>	Aerial parts	Rat	TNBS	Intrarectal	7 d	<i>n</i> = 10	DAI ↓, MPO ↓, reduced glutathione (GSH) content ↓, iNOS ↓, IL-1β ↓, IL-6 ↓, monocyte chemoattractant protein 1 (MCP-1) ↓, intercellular adhesion molecule 1 (ICAM1) ↓, IL-17 ↓, MUC-3 ↑, trefoil factor 3 gene (TFF)-3 ↑
[201]	<i>Ziziphora clinopoides</i>	Aerial parts	Mice	DSS	Oral	7 d before colitis induction	<i>n</i> = 6	Colon lipid peroxidation (LPO) ↓, total thiol molecules (TTM) ↑, total antioxidant capacity (TAC) ↑, NO ↑, TNF-α ↓, superoxide dismutase (SOD) ↑, catalase (CAT) ↑

[202]	<i>Lavandula intermedia</i> (cultivar Okanagan)	Essential oil	Mice	<i>Citrobacter rodentium</i>	Oral	5-10 d	-	Mortality and morbidity ↓, cecal damage ↓, damage of distal colon ↔, iNOS ↓, IFN-γ ↓, IL-22 ↓, macrophage inflammatory protein (MIP)-2α ↓
[203]	<i>Pisum sativum</i> (Green Pea)	Powdered fruit	Mice	DSS	Oral	9 wk	n = 7	DAI ↓, MCP-1 ↓, COX-2 ↓, IL-6 ↓, IFN-γ ↓, IL-17 ↓, iNOS ↓, MUC-2 secretion ↑, TFF-3 ↑, kruppel-like factor 4 ↑, sam-pointed domain Ets transcription factor-1 ↑, activating transcription factor 6 (ATF)-6 ↓
[33]	<i>Cannabis sativa</i>	Cannabidiol	Mice	Dinitrobenzene sulfonic acid (DNBS)	Intracolonic	6 d	-	DAI ↓, iNOS ↓, nitrite production ↓, IL-1β ↓, IL-10 ↑, anandamide & 2-arachydonylglycerol ↓, reactive oxygen species (ROS) formation ↓
[204]	<i>Cannabis sativa</i>	Cannabigerol	Mice	DNBS	Intracolonic	Preventive protocol: 6 d/ curative protocol: 2 d	-	Pre-treatment → DAI ↓, Fluorescein isothiocyanate (FITC)-conjugated dextran in the serum ↓, nitrite ↓ treatment → MPO ↓, SOD ↑, iNOS ↓, IL-1β ↓, interferon (INF)-γ ↓, IL-10 ↑
[34]	<i>Olea europaea</i> (olive)	Leaves	Rat	Acetic acid (AA)	Oral	3 d	n = 6	DAI ↓, TNF-α ↓, NO ↓, IL-1β ↓, IL-6 ↓, iNOS ↓, IL-2 ↓
[83]	Crude canola (rapeseed) oil	Phenolic compound 4-vinyl-2,6-dimethoxyphenol (canolol)	Mice	DSS	Oral	7 d	-	DAI ↓, COX-2 ↓, free 8-hydroxy-2'-deoxyguanosine (OHdG) in the plasma ↓, IL-12 ↓, TNF-α ↓, NO ↓
[37]	<i>Retama monosperma</i>	Aerial parts/ flavonoids	Rat	TNBS	Oral	48, 24 and 1 h prior to the induction of colitis & 24 h later	n = 10-11	DAI ↓, COX-2 ↓, iNOS ↓, p38 mitogen-activated protein kinase (MAPK) ↓

[38]	<i>Hibiscus rosa sinensis</i>	Leaves/ alkaloid, flavonoids, steroid and phenols	Mice and rat	AA	Oral	7 d before colitis induction	<i>n</i> = 6	DAI ↓, spleen enlargement ↓, white blood cell (WBC) count ↑, red blood cell (RBC) count ↑, hemoglobin (Hb) ↑, hematocrit ↑, platelet count ↑, SOD ↑, GSH ↑, LPO ↓, MPO ↓, nitrite/nitrate levels ↓, TNF-α ↓
[205]	Changtai granule	Traditional Chinese empirical formula comprised of Phellodendro Chinense, Sanguisorba officinalis , Euphorbia humifusa and polygonum hydropiper	Rat	TNBS	Oral	7 d	-	DAI ↓, MPO ↓, COX-2 ↓, iNOS ↓, Th1 cytokine response ↓, translocation of NF-κB in lamina propria mononuclear cells ↓
[206]	<i>Syringa vulgaris</i>	Verbascoside/ phenylpropano- id glycosides	Rat	DNBS	Oral	3 d	<i>n</i> = 10	DAI ↓, TNF-α ↓, IL-1β ↓, iNOS ↓, NO ↓, poly(ADP ribose) ↓, IκB-α levels in colon ↑, pro-matrix metalloproteinase (MMP)-2 ↑, MMP-9 ↑
[39]	<i>Curcuma longa</i>	Curcumin	Rat	TNBS	Oral	3 d before induction of IBD & was continued for 5 d after	<i>n</i> = 8	DAI ↓, TNF-α ↓, MPO ↓, NO ↓, colonic hydroxyproline & ceruloplasmin levels ↓, expression of MMP-1, MMP- 3 and tissue inhibitors of metalloproteinase 1 (TIMP)-1 ↓
[39]	<i>Ginkgo biloba</i>	Root	Rat	TNBS	Oral	3 d before induction of IBD & was continued for 5 d after	<i>n</i> = 8	DAI ↓, TNF-α ↓, MPO ↓, NO ↓, colonic hydroxyproline and ceruloplasmin levels ↓, expression of MMP-1, MMP- 3 and TIMP-1 ↓
[207]	<i>Cordyceps militaris</i> Grown on Germinated Soybeans (GSC)	Mycelia	Mice	DSS	Oral	2 or 9 d before colitis induction	<i>n</i> ≥ 15	DAI ↓, MMP-3 ↓, MMP-9 ↓, TNF-α ↓, iNOS ↓, p53 ↓
[208]	<i>Ficus bengalensis</i>	Stem bark	Rat	TNBS	Oral	21 d	<i>n</i> = 6	DAI ↓, colon mucosal damage index ↓, MPO ↓, MDA ↓, NO ↓, SOD ↑

[46]	<i>Vaccinium corymbosum</i> (blueberry)	Fruits/phenolic acids and flavonoids	Mice	DSS	Oral	14 d	<i>n</i> = 6	DAI ↓, COX-2 ↓, IL-1β ↓, p65 NF-κB ↓, IFN-γ ↓, iNOS ↓, MDA ↓, CAT ↑, SOD ↑, prostaglandin E2 (PGE2) ↑
[209]	<i>Hericium erinaceus</i> (Lion's Mane Medicinal Mushroom)	Mycelia	Mice	DSS	Oral	7 d	-	DAI ↓, MPO ↓, TNF-α ↓, IL-1β ↓, IL-6 ↓, NO ↓, MDA ↓, SOD ↓ in serum
[40]	<i>Panax notoginseng</i>	Root/saponin	Mice	AOM and DSS	Oral	15 d	<i>n</i> = 3	DAI ↓, COX-2 ↓, iNOS ↓
[75]	<i>Citrus nobilietin</i>	Nobiletin	Rat	TNBS	Intragastric	7 d (1 d after colitis induction)	-	MPO ↓, iNOS ↓, COX-2 ↓, myosin light-chain kinase (MLCK) ↓, NF-κB ↓, protein kinase B (Akt) phosphorylation ↓, trans epithelial electrical resistance ↓, inhibition of the Akt-NF κB-MLCK pathway
[66]	<i>Vaccinium corymbosum</i> (Portuguese blueberries)	Anthocyanin-rich fraction	Rat	TNBS	Intragastric	8 d	<i>n</i> = 8	DAI ↓, iNOS ↓, COX-2 ↓
[41]	<i>Malus sylvestris</i> (apple)	Fruit	Rat	AA	Oral	6 d	<i>n</i> = 5-6	iNOS expression ↓, COX-2 expression ↓, Copper Zinc (CuZn) SOD expression ↑ protein expression of iNOS ↓ in ulcerated area, COX-2 ↔ & 8-OHdG ↔
[210]	<i>Scutellariae baicalensis</i>	Oroxyloside	Mice	DSS	Intragastrically	10 d	<i>n</i> = 8	DAI ↓, MPO ↓, iNOS ↓, pro-inflammatory, cytokines in serum & colon ↓, peroxisome proliferator-activated receptor (PPAR)c ↑ → NF-κB ↓
[211]	<i>Rheum tanguticum</i>	Polysaccharide	Rat	TNBS	Intrarectal	5 d	<i>n</i> = 12	DAI ↓, NF-κB p65 ↓, TNF-α ↓, COX-1 ↔, COX-2 ↓, PGE2 ↑, iNOS ↓
[212]	<i>Hypericum perforatum</i> (St. John's Wort)	<i>Hypericum perforatum</i> extract	Rat	TNBS	Intraperitoneal	3 and 7 d treatments	-	DAI ↓, CAT ↓, GSH ↑, tissue NO ↓, MPO, glutathione reductase (GR), MDA, GSH-Px ↔

[42]	<i>Allium sativum</i> (garlic)	Diallyl sulfide (DAS) and diallyl disulfide (DADS)	Mice	DNBS + DAS DADS	Oral	2 d after first day of treatment	<i>n</i> = 10	<i>In vivo</i> → DAI ↓ <i>In vitro</i> → DADS → IL-6 ↓, hydrogen sulfide ↑ DAS → nitrite ↓, STAT-1 ↓, hydrogen sulfide ↑
[213]	<i>Avena sativa</i> (oat)	β-glucan	Mice	DSS	Intragastric	14 d	<i>n</i> = 20	DAI, TNF-α, IL-1β, IL-6, iNOS, NO, MDA, MPO ↓
[31]	<i>Eryngium duriae</i> subsp. <i>Juresianum</i> ; <i>Laserpitium eliasii</i> subsp. <i>Thalictrifolium</i> ; <i>Lavandula luisieri</i> , <i>Thapsia villosa</i>	Essential oils (EO)	Primary human chondrocyte & C2BBel	IL-1β or a cytokine mixture (IFN-γ, IL-1β TNF-α)	-	EO added 30 min before cytokine stimulation	-	EO of <i>L. luisieri</i> → iNOS ↓, p-IkB-α ↓ in both cell models EO of <i>E. duriae</i> subsp. <i>juresianum</i> → iNOS ↓, p-IkB-α ↓ in human chondrocytes EO of <i>L. eliasii</i> subsp. <i>thalictrifolium</i> & <i>O. maritimus</i> → iNOS ↓ in C2BBel cells EO of <i>T. villosa</i> → inactive in both cell types
[214]	<i>Rhizophora apiculata</i>	Whole plant	Mice	AA	Intraperitoneal	7 d	<i>n</i> = 6	SOD ↑, GSH ↑, LPO ↓, NO ↓, MPO ↓, lactate dehydrogenase (LDH) ↓, iNOS ↓, COX-2 ↓, translocation of NF-κBp65 & p50 subunits ↓
[215]	<i>Polygonum multiflorum</i>	2,3,5,4'-tetrahydroxystilbene-2-O-beta-d-glucoside (THSG)	Mice	AA+ mitomycin C	Oral	7 d and 24 d	<i>n</i> = 12	THSG (60 mg/kg) → DAI ↓, MPO ↓, MDA ↓, NO level ↓, iNOS ↓, SOD ↑ THSG (120 mg/kg) & 24th day of mitomycin C → > positive control, 5-aminosalicylic acid (5-ASA)
[94]	<i>Oryza sativa</i> L. (black rice)	Anthocyanin and rosmarinic acid	Mice	DSS	Oral	8 d	<i>n</i> = 8	Macroscopic damage ↓, microscopic damage ↓, body weight loss ↓, iNOS ↓, COX-2 ↓, IL-6 ↓, IL-1β ↓, TNF-α ↓
[67]	<i>Dioscorea alata</i>	Anthocyanidin- es	Mice	TNBS	Rectal	7 d	<i>n</i> = 10	Macroscopic damage ↓, microscopic damage ↓, body weight loss ↓, tight junction proteins ↑, MPO ↓, iNOS ↓, TNF-α ↓, IFN-γ ↓
[216]	<i>Patrinia scabiosaeifolia</i>	Root	Mice	DSS	Oral	7 d	<i>n</i> = 8	Macroscopic damage ↓, microscopic damage ↓, IL-6 ↓, IL-1β ↓, TNF-α ↓, iNOS ↓

[217]	<i>Morinda citrifolia</i> (noni)	Fruit juice/ flavonoids	Mice	DSS	Oral	9 d	<i>n</i> = 8	Microscopic damage ↓, IL-6 ↓, INF-γ ↓, NO ↓, MPO ↓
[201]	<i>Ziziphora clinopoides</i> (kahlioti)	Aerial parts	Mice	DSS	Oral	7 d	<i>n</i> = 6	TNF-α ↓, TAC ↑, TTM ↑, LPO ↓, NO ↓
[44][43]	<i>Camellia sinensis</i> (Black tea)	Theaflavin-3,30-digallate	Mice	TNBS	Oral	18 d	-	Macroscopic damage ↓, microscopic damage ↓, iNOS ↓, MPO ↓, TNF-α ↓, IFN-γ ↓, IL-12 p40 ↓, NFκB ↓
		Thearubigin	Mice	TNBS	Oral	18 d	-	Macroscopic damage ↓, microscopic damage ↓, iNOS ↓, O2- ↓, MPO ↓, IFN-γ ↓, IL-12 ↓, IL-4 ↓, NFκB ↓
[218]	<i>Picrasma quassiodes</i>	Dried branches/ alkaloids	Mice	TNBS	Gastric lavage	7 d	<i>n</i> = 10	Macroscopic damage, microscopic damage, body weight loss, MPO, TNF-α, IL-8, COX-2, iNOS ↓
[95]	<i>Aronia berries</i>	Berry extract/ polyphenols	Mice	DSS	Oral	10 d	-	Macroscopic damage, microscopic damage, body weight loss, TNF-α, IL-6, PGE2, NO, MAPK ↓
[199]	<i>Terminalia catappa</i>	Stem/phenolic compound	Rat	TNBS	Oral	9 d	-	Macroscopic damage ↓, microscopic damage ↓, NO ↓, IL-1β ↓, MUC2 ↑, MUC3 ↑
[45]	<i>Glycyrrhiza glabra</i> (liquorice)	Glabridin	Mice	DSS	Oral	7 d	-	Macroscopic damage, microscopic damage, body weight loss, iNOS, MPO, COX-2, TNF-α, IL-6 ↓
[219]	<i>Punica granatum</i> (pomegranate)	Extract/ phenolic compounds	Rat	DSS	Oral	30 d	<i>n</i> = 8	Macroscopic damage ↓, Bifidobacteria and Lactobacilli ↑, lipid peroxidation ↓, iNOS ↓, COX-2 ↓, P53 ↑, cluster of differentiation molecule (CD) 40 ↓, IL-1β ↓, IL-4 ↓

[220]	<i>Physalis peruviana</i>	Calyx/ flavonoids, terpenoids & glycosides	Rat	TNBS	Intraperitoneal	3 d in protective protocol and 15 d in therapeutic protocol	-	Macroscopic damage ↓, microscopic damage ↓, COX-2 ↓, iNOS ↓, MPO ↓, NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) ↓, IL-1β ↓, IL-6 ↓, IL-10 ↓, MUC2 ↑
[221]	<i>Perilla frutescens</i>	Whole plant	Mice	DSS	Oral	14 d (starting from 7 d before induction of colitis)	n = 6	NF-κB ↓, COX-2 ↓, iNOS ↓, cyclin D1 ↓, STAT-3 activation ↓, nuclear factor erythroid 2-related factor (Nrf)2 ↑, heme oxygenase-1 (HO-1) ↑, interferon regulatory factor 3 (IRF3) ↓, PE (10 mg/mL) in CCD841CoN human normal colon epithelial cells → TNF-α ↓, iNOS ↓, P-IκB α ↓, P-STAT-3 ↓, C-X-C Motif Chemokine Receptor 2 (CXCR)2 ↓

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corymbosum), rich in phenolic acids especially flavonoids, was shown to inhibit iNOS overexpression through the NF-κB signaling pathway.

***Panax notoginseng* (Burkill) F.H.Chen:** *Panax notoginseng* (*P. notoginseng*) is a well-known Chinese herbal medicine. An interesting character of *P. notoginseng* is its potential therapeutic effects on chronic diseases. The root extract of *P. notoginseng*, containing saponin, was found to exert inhibitory effects on iNOS and inflammatory cytokines^[40].

***Malus pumila* Mill.:** Apples (*Malus spp.*, *Rosaceae*) and their products, rich in polyphenols, have shown diverse biological activities and may contribute to a variety of beneficial health events such as protecting the intestine against inflammation initiated by IBD. The preventive effect of polyphenolic concentrated apple extract was illustrated in an acetic acid-induced IBD rat model, resulting in inhibition of iNOS overexpression through the NF-κB pathway^[41].

***Allium sativum* L.:** Plants of the genus *Allium* are known for their production of organosulfur compounds, which have marked biological and pharmacological properties. Garlic (*Allium sativum*) is one of the most widely used species, displaying a broad spectrum of beneficial anti-inflammatory effects. Diallyl sulfide and Diallyl disulfide are the main organosulfur compounds, with proved inhibitory effects on nitrite derivatives and pro-inflammatory elements involved in IBD pathogenesis^[42].

***Camellia sinensis* (L.) Kuntze:** *Camellia sinensis* (*C. sinensis*) leaves are rich in vitamins (B and C), minerals, polyphenols, caffeic acid, ferulic acid, tannins, and volatiles. *In vivo* studies showed that the polyphenol components of *C. sinensis*, theaflavin, and thearubigins, downregulated iNOS overexpression through the NF-κB pathway in oxidative-induced inflammatory complications such as IBD^[43,44].

***Glycyrrhiza glabra* L.:** Licorice, derived from the root of *Glycyrrhiza glabra*, is extensively used in traditional medicines for a variety of complications and ailments.

Licorice possesses immune-modulatory and adaptogenic properties, required for the pathogenesis of IBD. The ethanolic extract of this plant, rich in glabridin, was found to be effective in IBD as it attenuated pro-inflammatory elements and iNOS production^[45].

Phytochemicals

Table 2 depicts plant-derived compounds that affect IBD by modulating the NO pathway. Polyphenols are the most investigated plant-derived constituents with well-documented positive effects for IBD treatment *via* the NO pathway^[46]. According to their chemical structures and phenolic content, polyphenols are classified into several subgroups. This section mostly focused on the effects of these subgroups on the NO pathways.

Flavonoids: Flavonoids are natural products present in a wide range of vascular plant species. They function in several categories including protection against UV-light and phytopathogens (*i.e.*, phytoalexins in legumes), attraction of pollinators (*i.e.*, anthocyanins in berries), and reduction of reactive oxygen species (ROS) in conditions of oxidative stress (*i.e.*, quercetin and other flavonols)^[47]. Previous studies rigorously support the effect of flavonoids on suppressing various elements involved in innate immunity in a variety of hypersensitivity and inflammatory conditions including osteoarthritis, nephrotoxicity, photodamaged skin, diabetes mellitus, and IBD^[48-53]. As mentioned, iNOS is an inflammatory marker, creating a situation of oxidative stress by producing high amounts of NO, resulting in a slippery slope of ONOO⁻ formation, oxidative damage, nitration, and S-nitrosylation of certain biomolecules such as proteins, lipids, and DNA^[54].

During inflammation, flavonoids regulate/reduce NO production and iNOS expression *via* 2 main pathways; the NF- κ B and JAK/STAT signaling pathways^[55-57]. These pathways are stimulated during the inflammatory process, then macrophages are infiltrated to affected tissues. Thereafter, TLR-4 and INF- γ receptors are activated and induce the mentioned molecular cascades. Consequently, expression of iNOS is up-regulated. Flavonoids also downregulate the NO pathway, due to their ability to suppress elements of the above-mentioned pathways^[47].

The peroxisome proliferator-activated receptor γ (PPAR γ) was found to be a key participant in downregulation of iNOS^[58]. PPAR γ is a major transcription factor of lipid oxidation and metabolism genes in macrophages, and has anti-inflammatory activities. Apigenin, chrysin, and kaempferol were found to especially reduce iNOS expression *via* PPAR γ activation *in vitro*^[59]. Park *et al*^[60] suggested that beyond NF- κ B inhibition, the anti-oxidant activities of flavonoids must be mediated by other mechanisms. It is reported that trimeric flavonoids exhibit stronger anti-inflammatory and anti-oxidant properties than monomeric flavonoids. Trimeric flavonoids activate the NF- κ B pathway, while monomeric flavonoids were shown to have a suppressive effect.

Several protein docking simulation analyses have proposed that flavonoids such as silibinin and deguelin, can directly bind iNOS and are able to suppress iNOS activity. Therefore, a number of flavonoids might directly bind iNOS and inhibit its functions, in a way other than modulating its expression at gene level^[61,62]. Overall, flavonoids significantly diminish pathologic lesions in colonic tissue, attributed to their anti-inflammatory and antioxidant effects, resulting in NO reduction.

Anthocyanins: Anthocyanins are an important subcategory of flavonoids, available in many fruits and vegetables with a prominent red, blue, or purple hue. Anthocyanins were shown to effectively suppress inflammation and tumorigenesis processes in different cell lines^[63-65]. A significant decrease was reported in the expression levels of TNF- α and iNOS, when anthocyanin-rich fractions (ARF) of purple yam (*Dioscorea alata* L.) and Portuguese blueberries (*Vaccinium corymbosum* L.) were orally administered to animals. The ARF prepared from the latter fruit reduced iNOS expression as effectively as 5-aminosalicylic acid (5-ASA) at a molar anthocyanin concentration approximately 30 times lower than that of 5-ASA^[66,67].

Cardamonin: Oral administration of Cardamonin, a chalconoid produced in members of the *Alpinia* genus, reversed the upregulation of TLR-4 and cytokine receptors along with the cascade of proteins downstream to these receptors (*i.e.*, myeloid differentiation factor 88, IL-1 receptor-associated kinase-1, inhibitor κ B α , and inhibitor κ B kinase- α/β , as well as MAPK and c-Jun NH2-terminal kinase), resulting in inhibition of the nuclear localization of NF- κ B p65 and inactivation of the MAPK pathway. Cardamonin also suppressed the expression of their target genes, *i.e.*, iNOS^[68].

Luteolin: Luteolin, a yellow, naturally occurring flavone, interferes with iNOS

Table 2 Plant-derived compounds affecting inflammatory bowel disease by modulating nitric oxide pathways

Ref.	Phytochemical	type of animal	Model of IBD	Route of administration	Duration of treatment	Numbers of animals in intervention group and control group	Outcomes
[71]	Naringenin (25, 50, 100 mg/kg per day)	Rat	Acetic acid (AA)	Transrectal	7 d before colitis induction	<i>n</i> = 6	Disease activity index (DAI) ↓, total glutathione sulphadryls (T-GSH) ↑, non-protein sulphadryls ↑, DNA, RNA and total protein content ↑, nitrit oxide (NO) ↓, catalase (CAT) ↑, superoxide dismutase (SOD) ↑, tumor necrosis factor (TNF)-α ↓, interleukin (IL)-1β ↓, IL-6 ↓
[82]	Eupatilin (ethanol extract of aerial parts of <i>Artemisiae herba</i> , EIE) and quercetin-3-β-D-glucuronopyrano side from <i>Rumex aquaticus</i> (EIQ) (EIE, 100 mg/kg & EIQ, 30 mg/kg)	Rat	2,4,6-trinitrobenzene sulfonic acid (TNBS)	Oral	48, 24 and 1 h prior to the TNBS instillation and again 24 h later	<i>n</i> = 6	DAI ↓, myeloperoxidase (MPO) ↓, NO ↓, TNF-α ↓, total glutathione sulphadryls (GSH) ↑, malondialdehyde (MDA) ↓
[74]	Naringin (20, 40, or 80 mg/kg)	Rat	AA	Oral	12 d (8 d before colitis induction and 4 d after)	<i>n</i> = 6	DAI ↓, spleen weight ↓, white blood cell (WBC) ↑, red blood cell (RBC) ↑, hemoglobin (Hb) ↑ & platelet ↑, lactate dehydrogenase (LDH) ↓, alkaline phosphatase (ALP) ↓, SOD ↑, GSH ↑, Colon lipid peroxidation (LPO) ↓, NO ↓, MPO ↓, xanthine oxidase activity ↓, protein carbonyl content ↓, the number of unwinded double strand DNA ↓
[222]	Oligonol (0.5 and 5 mg/kg/d)	Mice	Dextran sulfate sodium (DSS)	Oral	7 d before colitis induction	<i>n</i> = 5	DAI ↓, IκBα phosphorylation & degradation ↓, p65 phosphorylation & nuclear translocation ↓, cyclooxygenase (COX-2) ↓, iNOS ↓, expression of antioxidant enzymes ↑, colon carcinogenesis ↓, the incidence and the multiplicity of colonic adenoma ↓

[223]	Algal meroterpenoid hydroxy-11-methylmentadione (1, 10 & 20 mg/kg)	Mice	DSS	Oral	7 d after colitis induction		DAI ↓, MPO ↓, TNF-α ↓, IL-1β ↓, IL-10 ↓, COX-2 ↓, iNOS ↓
[224]	Fraxinellone	Mice	DSS and lipopolysaccharide (LPS)	intraperitoneal	9 d	n = 10	DAI ↓, MPO ↓, alkaline phosphatase (ALP) ↓, glutathione ↑, IL-1β ↓, IL-6 ↓, IL-18 ↓, TNF-α ↓, inhibition of cluster of differentiation molecule 11B (CD11B)+ macrophage infiltration, ICAM1 ↓, vascular cell adhesion molecule 1 ↓, iNOS ↓, COX-2 ↓, NO ↓, NF-κB signaling ↓ & NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome ↑
[79]	Isoquercitrin (1 and 10 mg/kg/d)	Rat	DSS	Oral	14 d (DSS induced the second half)	n = 8	Colon shortening ↓, COX-2 ↓, iNOS ↓, tissue healing did not encompass rectum
[225]	Oridonin (5.0 and 7.5 mg/kg)	Mice	TNBS	intraperitoneal	7 d	n = 3-9	DAI ↓, TNF-α ↓, interferon (INF) ↓, IL-17A ↓, iNOS ↓, COX-2 ↓, <i>in vitro</i> lymphocyte proliferation ↓, NF-κB p65 expression & activity ↓
[68]	Cardamonin (20, 50, and 100 mg/kg)	Mice	DSS	Oral	2 d before DSS treatment & 7 d after	n = 10	NO ↓, TNF-α ↓, IL-6 ↓, toll like receptor (TLR)-4 ↓, myeloid differentiation factor (MDF) 88 ↓, IL-1 receptor-associated kinase-1 ↓, IκBα ↓, IκBK-α/β ↓, mitogen-activated protein kinase (MAPK) ↓, c-Jun NH2-terminal kinase ↓, nuclear translocation of NF-κB p65 ↓

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expression in IBD models by inhibiting elements of the NF-κB cascade as mentioned above^[69]. Luteolin significantly inhibited IL-8 production, COX-2 and iNOS expression, and cytokines-induced NO overproduction; indicating that luteolin negatively modulates the key inflammatory signaling cascades underlying intestinal inflammation. Mechanistically, inhibition of the JAK/STAT pathway was identified as a critical mechanism by which luteolin exerts its intestinal anti-inflammatory action^[70].

Naringenin and naringin: Naringenin and naringin, the glycosidic form of

naringenin, belong to the flavanones and are frequently found in grapefruit. These compounds were shown to decrease the colonic level of NO and inflammatory cytokines^[71,72]. Moreover, naringin reduces colonic xanthine oxidase level, which catalyzes the conversion of nitrite, both the physiological storage pool of NO and its metabolites^[73]. Concerning NO reduction, pre-treatment with 50 mg/kg/d of naringenin showed efficiency comparable to Mesalazine (300 mg/kg/d)^[71].

Nobiletin: Nobiletin is a widely distributed O-methylated flavone found in citrus peels, which has recently attracted attentions due to its anti-insulin resistance, anti-inflammatory, and anti-cancer characteristics^[74]. In addition to decreasing the nuclear localization of NF- κ B, nobiletin regulated the tissue production of NO through an Akt-dependent manner. Oral treatment of nobiletin (40 mg/kg) was shown to be as potent as 100 mg/kg of Sulfasalazine, a first-line drug in IBD treatment^[75].

Quercetin and isoquercetin: Quercetin, the most widely distributed flavonoid, has been shown to suppress LPS-induced IKK, NF- κ B and AP-1 activation; and the IFN- γ -induced NF- κ B, STAT1, and interferon regulatory factor-1 (IRF-1) activation *in vitro*, almost all of which are upstream of the NF- κ B and JAK/STAT signaling pathways. Quercetin also induces heme oxygenase-1 (HO-1) expression *via* activation of tyrosine kinase and MAPK. Quercetin was shown to partly downregulate iNOS expression through this pathway^[76]. Suppression of PI3K/AKT might reduce the nuclear translocation of NF- κ B and the subsequent increase in iNOS expression^[77,78].

Isoquercetin, the 3-O-glucoside of quercetin is present in fruits such as mango, and has been shown to repress iNOS expression in IBD models, in a dose-dependent manner^[79]. However, isoquercetin displayed little to no effect on histological damage and the iNOS level in lower segments of the colon, where the damage was considerably severe, suggesting that the isoquercetin effect might be correlated with severity and histology of target tissues^[79].

Wogonoside: Wogonoside is a bioactive flavonoid derived from the root of *Scutellaria baicalensis* Georgi. This glucuronide metabolite of wogonin has been shown to possess anti-inflammatory and anticancer effects. Recent studies revealed that NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome are implicated in IBD, mainly by inducing IL-1 β production. To date, only limited agents have been nominated to target both NF- κ B and NLRP3 inflammasome in IBD^[80]. In DSS-induced colitis mice, wogonoside alleviated body weight loss, colon length shortening, colonic pathological damage, inflammatory cells infiltration, myeloperoxidase (MPO) and pro-inflammatory mediators levels, and iNOS activity. Furthermore, this compound reduced IL-1 β , TNF- α , and IL-6 production, and downregulated the mRNA expression of pro-IL-1 β and NLRP3 in phorbol myristate acetate (PMA)-differentiated monocytic THP-1 cells, through suppression of NF- κ B and NLRP3 inflammasomes. Wogonoside also repressed iNOS expression, twice more potent than 5-ASA, by suppressing both NF- κ B and NLRP-3 inflammasomes, which were not targeted by 5-ASA^[81].

Other flavonoids: A number of flavonoids have also been reported to reduce iNOS expression and inflammatory cytokines in IBD models such as (1) Rutin (the glycoside combining the flavonol quercetin and the disaccharide rutinose found in citrus fruits but not quercetin itself)^[81]; (2) Glabridin (an isoflavone of the root extract of licorice)^[45]; (3) Eupatilin (an O-methylated flavone from the aerial parts of *Artemisiae herba*); and (4) Quercetin-3- β -D-glucuronopyranoside (isolated from *Rumex aquaticus*)^[82].

Other polyphenols: In this section, we discuss other polyphenolic compounds rather than flavonoids.

Canolol

A major component of crude canola oil called canolol, has been put in the spotlight due to its anti-mutagenesis roles. Canolol was shown to affect IBD and NO production in the manner discussed above^[83]. It was reported that following canolol treatment, IL-12, TNF- α , COX-2, iNOS, and the oxidative responding molecules (*i.e.*, HO-1) were suppressed^[83].

Curcumin

Hydroxycinnamic acids are a subcategory of polyphenols. Among these compounds, curcumin a bright yellow curcuminoid found in turmeric, is the main spice in curry, and is considered as an antioxidant, anti-inflammatory, and anti-tumorigenesis substance. In addition to suppressing NO production and iNOS expression during reducing inflammation in IBD models^[39], curcumin plays an anti-epileptic role in the central nervous system by downregulating neuronal NOS, improving endothelial

dysfunction and vascular remodeling through upregulation of eNOS^[84-86]. It has also been reported that the anti-inflammatory effect of curcumin has been implicated in suppression of the protein components of the NF- κ B and JAK/STAT pathways^[51,86,87].

Gallic acid, thea-3,3'-bigallate, and thearubigin

Among the polyphenols, hydrobenzoic acids have received considerable attentions. Gallic acid itself and its derivatives such as thea-3,3'-bigallate and thearubigin (a polymer of epigallocatechin and epigallocatechin gallate found in black tea), were shown to modulate iNOS expression and NF- κ B suppression^[45,46,88]. In addition, gallic acid acts through the IL-6/STAT-3 signaling pathway, not *via* iNOS expression^[88,89].

Oligonol

Oligonol is a lychee-fruit-derived low molecular weight polyphenol containing catechin-type monomers and oligomers with beneficial effects on memory in amyloid β -induced Alzheimer's disease models, and reduces tissue injury in various organs by inhibiting the expression of NF- κ B p65, COX-2, and iNOS^[90,91]. It was shown that oligonol improved inflammation through downregulation of iNOS expression and NO production, although the compound enhanced cardiac health by increasing NO production and vasodilation, which was mediated by eNOS upregulation^[91,92]. Oligonol can mediate IBD symptoms mainly *via* iNOS suppression^[93].

Rosmarinic acid

Rosmarinic acid is abundantly present in phenolic acid-rich species such as black rice and Aronia berry. Oral administration of rosmarinic acid ameliorated colonic inflammation and downregulated iNOS expression^[94,95]. Moreover, rosmarinic acid reduced IL-6, IL-1 β , and IL-22 expression, and suppressed the protein levels of COX-2 and iNOS in IBD by inhibiting the NF- κ B and STAT-3 signaling pathways^[96].

Dairy products

Therapeutic dietary products have long been of interest in mitigating inflammation. For instance, goat cheese whey; a by-product of the cheese-making process, is rich in amino acids threonine and cysteine, and oligosaccharides such as sialic acid; which can act as an antioxidant with considerable immunomodulatory function^[97,98]. In addition to increasing mucin synthesis by threonine and cysteine^[99,100], it can modulate the colonic flora in a murine model of colitis^[100]. In acetic acid-induced colitis rats, the anti-oxidative and anti-inflammatory properties of goat cheese whey have been shown to reduce iNOS expression, comparable to Sulfasalazine^[101]. Whether specific component/s of goat cheese whey is responsible for such effects requires clarification^[101].

It has been demonstrated that glycomacropeptide, a product of the enzymatic hydrolysis of casein, can have immunomodulatory effects by altering the colonic bacterial population, *i.e.*, accommodating host-friendly microorganisms and confronting pathogens^[102-104]. Pre-treatment of colitis rats with glycomacropeptide, inhibited pro-inflammatory cytokines production, iNOS expression, and improved anorexia^[105].

Probiotics and prebiotics

Although various data suggest that intestinal microorganisms trigger inflammation, and the efficacy of antibiotics is being clarified in IBD subjects; it seems the aberrant immune response to intestinal antigens plays a major role in the pathogenesis of IBD. In this regard, extensive research on commensal flora has revealed noticeable variations in the composition of gut microbiota in IBD patients compared with healthy controls^[106-108], active phases of IBD compared with inactive phases, and between the parts of the intestine affected by IBD^[109-111]. During past decades, ingestion of live microorganisms available as probiotics^[112] or non-digestible substrates for selective microorganisms known as prebiotics^[113], has been introduced as a method of altering the intestinal microbiome and to potentially prevent or reduce inflammation in IBD^[114]. Herein, we review evidence on the efficiency of pro- and pre-biotics in IBD treatment, specifically through modulation of NO production. Overall, it seems that pro- and pre-biotics attenuate NO production by suppression of the I κ B/NF- κ B pathway^[115], *i.e.*, *via* I κ B- α degradation and ubiquitination in epithelial cells^[116,117]. The anti-inflammatory properties of probiotics may be related to the suppression of proteasome function and inhibition of the transmission of complexes shaped by NF- κ B and PPAR- γ from the nucleus^[118]. In addition, IL-10 secretion and the suppression of dendritic cells-induced IL-12 secretion attenuated the immunomodulatory effects and iNOS activity^[118].

***Lactobacillus farciminis*:** *L. farciminis* has been shown to release NO *in vitro*. In 2004,

Lamine *et al*^[119] showed that oral administration of *L. farciminis* in a 2,4,6-trinitrobenzene sulfonic acid (TNBS) model of rat colitis, similar to sodium nitroprusside, led to intraluminal NO release, alleviated the macroscopic evidence of colitis, and attenuated iNOS and MPO activities. In 2006, Peran *et al*^[120] designed a study to investigate the potency of *L. fermentum* in the TNBS model of rat colitis. Treatment with *L. fermentum* promoted *Lactobacillus* species growth and short-chain fatty acids (SCFAs) production, reduced microscopic colitis, extenuated oxidative stress, and ameliorated TNF- α secretion and iNOS expression. They subsequently performed a comparative analysis of the effectiveness of probiotics in the same model, in which treatment with *Bifidobacterium lactis*, also known as *L. acidophilus*, reduced iNOS expression, and prevented intestinal inflammation and diarrhea^[121]. However, *L. casei* seemed to have no significant effect on iNOS expression^[121].

B. lactis was shown to transiently activate NF- κ B expression and p38 MAPK, the bacterium also inhibited the expression of iNOS and COX-2, and TNF- α production. This was achieved by facilitating a cross-talk between the intestine epithelial cells and immune cells^[122], indicating the anti-inflammatory effect of *B. lactis*. On the other hand, *L. acidophilus* and *L. fermentum*, secondary to a decrease in inflammatory cytokines release and neutrophil activation, reduced iNOS expression and oxidative stress^[120]. In contrast, *L. farciminis*, seems to exert its anti-inflammatory effect mainly by generating NO in the intestine, and partly through reducing the release of pro-inflammatory cytokines, and by enhancing the barrier integrity and modification of intestinal flora^[123].

In DSS-induced colitis mice, administration of *L. plantarum* AN1 strain cells, which were derived from the fermented fish aji-narezushi, enhanced endogenous *Lactobacillus* growth, especially *L. reuteri*, and protected against colitis with a significant effect on mucosal damage^[124]. On the other hand, *in vitro* administration of both live and heated *L. plantarum* AN1 strains to murine macrophage RAW264.7 cells, improved the anti-inflammatory effect by reducing NO secretion^[124], supporting the outcomes of previous studies.

In addition to the beneficial effects of *Lactobacillus* in reducing NO production in animal models of colitis, the protective effects of *L. rhamnosus* GG on normal human colon epithelial cells and murine macrophages, by increasing iNOS expression, has been reported^[125]. Thus, it appears that *Lactobacillus* may be beneficial in alleviating colitis by modulating iNOS expression. In the DSS model of colitis^[126], oral administration of *Rhodobacter sphaeroides* extract (LycogenTM), reduced pro-inflammatory cytokines and NO production, decreased colonic bacteria, and prevented weight loss and colon shortening, while improving survival^[126].

More recently, combination therapy with probiotics has been examined in animal models of colitis. A combination of four live bacterial strains (*L. acidophilus*, *L. plantarum*, *B. lactis* and *B. breve*) form a probiotic cocktail named "Ultrabiotique". It was shown that oral administration of Ultrabiotique in DSS-induced colitis, attenuated microscopic evidence of inflammation, reduced NO production, as measured in the supernatants of peritoneal macrophages (PMQ) cultures^[127]. Later, a study by Toumi *et al*^[128] demonstrated that Ultrabiotique treatment ameliorated plasma NO and IFN- γ production in association with reduced expression of colonic TLR-4, iNOS and NF- κ B in DSS-induced colitis. LPS-induced TLR-4 stimulation, activated the NF- κ B pathway, thereby, inducing iNOS expression. On the other hand, LPS-induced production of IFN- γ leads to the activation of IRF-1 and NF- κ B. *In vivo*, co-localization and interaction of IRF-1 and NF- κ B in the macrophage nucleus, physically bends the iNOS promoter DNA and leads to NO production^[129]. In this study, Ultrabiotique significantly reversed these mechanisms.

Kefir, a natural beverage consisting of a fermented dairy product obtained by exposing milk to yeast and bacteria; composed of *Lactobacillus*, *Acetobacteria*, *Streptococcus* and yeasts; attenuated colitis in DSS mouse model by extenuating pro-inflammatory cytokines and NO production^[128]. In a study by Soufli *et al*^[130] the laminated layer of *Echinococcus granulosus* cyst increased IL-10 expression, and decreased the expression of TNF- α , IFN- γ , NF- κ B, and iNOS, thus, improving colitis. Helminth antigens from organisms such as *Trichuris suis* have previously been used in IBD subjects; however, the underlying mechanisms are undetermined^[131-133], investigations into their potential to relieve inflammation in IBD are warranted.

In addition to direct anti-inflammatory effects of bacterial antigens, probiotic products may have such effects. Fermentation of water-soluble fibers by anaerobic bacteria leads to SCFA production. For instance, hydrolyzation and fermentation of inulin, a natural beta-fructan extracted from many types of plants, by microbiota and *Lactobacilli* in the intestinal lumen results in SCFAs formation (*i.e.*, butyric acid). It was shown that inulin suppressed inflammation in DSS-induced colitis rats, at least partly mediated by reducing NO production^[127]. Previous studies have shown that SCFAs significantly suppressed pro-inflammatory cytokines expression in intestinal cells *via*

downregulation of NF- κ B^[134,135]. Arribas *et al*^[136] developed a caramel with a high content of difructose dianhydrides and their glycosylated derivatives, cyclic fructans that were shown to provide an appropriate environment for *Lactobacillus* and *Bifidobacterium* species. In addition, the intestinal microbiota is able to produce SCFAs by fermentation of DFAs, and can further promote their anti-inflammatory effects by reducing iNOS expression.

Animal oils

The advantage of polyunsaturated fatty acids (PUFAs) intake in IBD was elucidated by epidemiologic studies in Eskimos^[137] and by lower levels of PUFAs in patients' sera^[138]. Although, data are conflicting, most of the studies support the efficiency of PUFAs in IBD^[137]. PUFAs are able to attenuate inflammation, as in IBD, by altering the production of eicosanoids and COX-2, and by modulating PPAR- γ and NF- κ B^[139-143]. The inefficacy of omega-3 PUFAs has been reported in a study on protection against IBD, which was in contrast to conjugated linoleic acid (CLA)^[143].

Omega-6 PUFAs such as (17S)-hydroxy-docosapentaenoic acid, but not (10, 17S)-dihydroxy-docosapentaenoic acid, exhibited inhibitory effects on iNOS expression in a DSS model of colitis, as well as predominating M2 macrophages with anti-inflammatory properties *in vitro*^[144]. Additionally, (5E,7Z,10Z,13Z,16Z,19Z)-4-Hydroxy-5,7,10,13,16,19-docosahexaenoic acid, a potential agonist of PPAR- γ with antidiabetic property^[145], has been shown to modulate colitis through suppression of iNOS. Although, these effects are independent of PPAR- γ inhibition^[146].

Amino acids

Glutamine: Glutamine at concentrations above 0.5 mmol/L reduced NF- κ B nuclear transportation, iNOS expression, and attenuated colitis severity^[147]. Indeed, the intrarectal administration of glutamine has been associated with less intestinal damage and reduced the expression of STAT-1, STAT-5, and NF- κ B, decreased pro-inflammatory cytokines (*i.e.*, IL-8 and IL-6) production, and enhanced IL-10 in an IBD model^[148].

L-Arg: Administration of L-Arg enhanced the survival time of colitis animals, while reducing the expression of iNOS and NF- κ B. However, different studies have reported various results on the beneficial effect of L-Arg on the colon^[149,150].

Synthetic molecules

Previous studies showed that NF- κ B inhibitors directly suppress the expression of NF- κ B dependent pro-inflammatory mediators, including iNOS. Therefore, blockade of the NF- κ B signal transduction pathway may be one of the major mechanisms underlying several synthetic molecules in management of IBD. Hence, the following sections will discuss studies in which NF- κ B/NO signaling helped to improve IBD complications (Table 3).

NF- κ B-NO dependent synthetic molecules

To date, numerous "NF- κ B and NO inhibitors" have been introduced with potentially beneficial effects in colitis treatment^[151,152]. Notably, the NF- κ B inhibitory effects of these molecules are mostly due to the blockade of NF- κ B translocation to the nucleus, either by inhibiting P65 or I κ B degradation.

COG112: It is known that Apolipoprotein E has immunomodulatory effects and synthetically derived Apolipoprotein E-mimetic peptides were found to be useful in models of sepsis and neuroinflammation. For example, one of these peptides, COG112, was shown to cause a significant reduction of iNOS expression in a colitis model^[153]. COG112 also improved the clinical parameters of survival, body weight, colon weight, and histologic injury in these animals. Moreover, COG112 inhibited colon tissue iNOS, keratinocytes, TNF- α , IFN- γ , and IL-17 mRNA expression, and reduced the nuclear translocation of NF- κ B. The IKK activity was also reduced, a necessary factor for activation of the canonical NF- κ B pathway^[153].

Dexamethasone: Dexamethasone is a corticosteroid, and exhibited a predictable positive effect on colitis-induced colon damage, which was correlated with reduced iNOS expression and NF- κ B activity. This effect was even stronger when dexamethasone was administered in particle or microsphere form^[151,152].

Pioglitazone: Pioglitazone is a PPAR γ ligand, approved for diabetes treatment. Pioglitazone was also found to be an NF- κ B-DNA binding inhibitor, allowing a reduction in iNOS expression and inflammation. Moreover, PPAR γ itself can bind NF- κ B and block its normal function, hence, reducing iNOS expression and other inflammatory end products of the NF- κ B pathway^[154,155].

Table 3 Synthetic compounds affecting inflammatory bowel disease by modulation of nitric oxide pathways

Ref.	Type of animal	Model of IBD	Intervention	Duration of treatment	Numbers of animals in intervention group and control group	Outcomes
[226]	Rat	Dextran sulfate sodium (DSS)	Dinitrate-barbiturate (rectally twice daily)	5 d	<i>n</i> = 12	Matrix metalloproteinase (MMP)-9 activity ↓, disease activity ↓, colonic injury ↓
[227]	Rats	Lipopolysaccharide (LPS)	Ursodeoxycholate (gavage)	4 d	<i>n</i> = 4	Circulating nitrite/nitrate ↓, intestinal epithelial inducible nitric oxide synthase (iNOS) activity ↓, colonic injury ↓
[177]	Rat	Acetic acid (AA)	N-Acetylcysteine (NAC) (100 mg/kg for 7 d, 20 mg/kg for 2 d) (intraperitoneal, intracolonic)	2 d, 7 d	-	100 mg/kg NAC → tissue myeloperoxidase ↓, glutathione ↓, NO ↓, colonic injury ↓ 20 mg/kg NAC → no protective effects
[229]	Rat	2,4,6-trinitrobenzene sulfonic acid (TNBS), AA	NG-nitro-L arginine methyl ester (L-NAME)	accompanied by TNBS or 7 d before AA	<i>n</i> = 55	TNBS-treated rats → tissue injury ↓, lesion area ↓, colonic weight ↓, myeloperoxidase activity ↓, nitric oxide synthase (NOS) activity ↓ 24 hours after AA + capsaicin pretreated rats → tissue injury ↓, lesion area ↓, colonic weight ↓, NOS activity ↓ TNBS + L-NAME treated rats → mean arterial blood pressure was higher than in TNB treated rats
[228]	Mice	Dinitrobenzene sulfonic acid (DNBS)	<i>Trichinella spiralis</i> antigens (helminth ags), (rectal submucosal)	5 d before DNBS induction	<i>n</i> = 6-8	Macroscopically and histologically colitis ↓, mortality rate ↓, MPO activity ↓, IL-1β production ↓, inducible nitric oxide synthase (iNOS) expression ↓, IL-13 ↑, transforming growth factor beta (TGF)-β ↑, TH2 dominance
[170]	Human mixed mono- nuclear cells (MMCs) co-cultured with HT-29 cells from UC patients	IFN-γ and LPS	Budesonide or prednisolone (corticosteroids)	Incubation or Pre-treatment	-	Nitrite content ↓, iNOS expression ↓
[191]	Rat	TNBS	Arginine-Glycine-Aspartic acid (RGD)-functionalized silk fibroin nanoparticles (SFN) (intrarectal, 1 mg/rat)	7 d	<i>n</i> = 10	Adhesion of integrins of the cell surface to the extra-cellular matrix of connective tissue ↓ → leukocyte recruitment to the inflamed intestinal tissue ↓ → iNOS expression ↓

[179]	Mice	DSS	Pravastatin, an 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase inhibitor, (intraperitoneal, 1 mg/kg)	10 d	<i>n</i> = 4-9	Cachexia ↓, hematochezia ↓, intestinal epithelial permeability ↓ with no effect on serum cholesterol, colonic injury ↓, expression of mucosal vascular addressin cell adhesion molecule 1 (MAdCAM-1) ↓, mucosal endothelial nitric-oxide synthase (eNOS) mRNA degradation ↓, eNOS expression ↑, protective effects of pravastatin in DSS-induced colitis were not found in eNOS-deficient mice
[153]	Mice	Pathogen <i>Citrobacter rodentium</i> as an infection model and DSS as an injury model	Antennapedia-linked Apolipoprotein E-mimetic peptide COG112, (intraperitoneal)	Concurrent with induction of colitis, during induction plus recovery, or only during the recovery phase of disease	<i>n</i> = 4	<i>C. rodentium</i> treated mice→ improving the clinical parameters of survival, body weight loss, colon weight, histologic injury, expression of iNOS & the CXC chemokine keratinocytes (KC) & macrophage inflammatory protein (MIP)-2, more effective in iNOS-deficient mice, DSS treated mice→ body weight loss ↓, colon length ↓, histologic injury ↓, iNOS ↓, KC ↓, TNF-α ↓, IFN-γ ↓, IL-17 mRNA expression ↓, nuclear translocation of NF-κB ↓, IKK kinase (IKK) activity ↓
[192]	Mice	DSS	3,3-Diindolylmethane (oral)	7 d, commencing at the same time DSS exposure began	<i>n</i> = 5	Number of iNOS- & COX-2-producing cells ↓
[147]	Rat	DSS	Glutamine (oral)	7 d with DSS	<i>n</i> = 13	Cytokine-induced iNOS expression ↓, nuclear translocation of NF-κB p65 subunit ↓, cellular heat shock proteins (HSP)25 & HSP70 in a dose-dependent manner ↑
[180]	Rat	TNBS	Lactulose (oral)	2 wk before TNBS administration	<i>n</i> = 10	MPO activity ↓, colonic TNF-α ↓, leukotriene B4 ↓, iNOS expression ↓, levels of Lactobacilli and Bifidobacteria species in colonic contents ↑
[229]	Rat	Iodoacetamide	NG-nitro - L-NAME (oral)	21 d	<i>n</i> = 9-16	lesion area ↓, NOS activity ↓

[200]	Mice	DSS	GL-V9, a synthesized flavonoid derivative (intragastric)	From day 1 to day 10	-	Inflammatory cells infiltration↓, myeloperoxidase (MPO) activity ↓, iNOS activity ↓, ROS & MDA generation ↓, SOD ↓, GSH reservoir ↑, pro-inflammatory cytokines production in serum & colon ↓; pro-inflammatory cytokines ↓, ROS production ↓, antioxidant defenses ↑ in mouse macrophage RAW264.7 cells by promoting thioredoxin-1 expression
[159]	Mice	DSS	Glucosamine oligomers (Chitoooligosaccharid-es) (oral)	5 d	<i>n</i> = 8	Number of positive areas of iNOS & nuclear factor (NF)-κB staining in the colonic epithelium ↓
[27]	Mice	DSS	Nitrite (1 mmol/L) or nitrate (10 mmol/L) (oral)	7 d	<i>n</i> = 27-29	Nitrite (1 mM) → DAI score↓, colon length ↑, iNOS expression ↓, histopathology ↓, DSS-induced decrease in colonic mucus thickness↓, goblet cell abundance ↑. Nitrate (10 mM)→ DAI-score ↓
[176]	Rats, mice	TNBS and DSS	Doxycycline (oral)	5 d after the first DSS colitis induction	<i>n</i> = 10-21	Macrophages → IL-8 production ↓ by intestinal epithelial cells & NO production ↓. TNBS-colitic rats (5, 10 and 25 mg/kg) → DAI score ↓, colonic tissue damage ↓, mRNA expression of IL-6, TNF, IL-17, intercellular adhesion molecule 1 (ICAM1), iNOS & MCP-1 ↓, partial restoration of the mRNA levels of markers of intestinal barrier function (ZO-1, occludin & mucin (MUC)-3
[173]	Ulcerative Colitis (UC) and Crohn's Disease (CD) patients	-	Corticosteroids (Sulfasalazine and Azathioprine) (intravenous)	-	(1) UC treated with high dose corticosteroids (6 patients, 10 blocks); (2) UC patients who had never received corticosteroids (10 patients, 16 blocks); (3) CD treated with high dose corticosteroids (12 patients, 24 blocks); (4) Non-inflammatory, non-neoplastic controls (4 patients, 6 blocks)	Immunostaining with an antibody raised against the C terminal end of iNOS for NOS→ diffuse in UC & patchy in CD in epithelial cells & was most intense near areas of inflammation, Non-inflamed epithelium showed no immunoreactivity, treatment with corticosteroids made no difference to the amount of NOS

[162]	Rat	TNBS	Telmisartan (angiotensin II receptor antagonist) (oral, 10 mg/kg)	10 d before TNBS and until day 4 of TNBS	<i>n</i> = 8	DAI score ↓, colon weight/length ratio ↓, macroscopic damage ↓, histopathological findings ↓. Inflammation ↓, leukocyte migration ↓, TNF-α ↓, prostaglandin E2 (PGE2) ↓, MPO activity ↓, restoration of IL-10 mRNA and protein expression of NF-κB p65 ↓, mRNA expression of COX-2 and iNOS ↓, peroxisome proliferator- activated receptor (PPAR)-γ ↑, oxidative stress ↓ [lipid peroxidation (LPO) ↓, NO ↓, GSH ↑, TAC ↑, SOD ↑, glutathione peroxidase activity ↑], apoptosis ↓ (mRNA, protein expression and activity of caspase-3 ↓, cytochrome C and Bax mRNA ↓, Bcl-2 ↓)
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IBD: Inflammatory bowel disease.

Tropisetron: Tropisetron is a serotonin 5-hydroxytryptamine 3 receptor antagonist and is mainly used as an antiemetic agent. Tropisetron was shown to have an anti-inflammatory effect *via* PPARγ upregulation, resulting in NF-κB blockade and diminishing NO production^[156]. This drug reduced the expression of β-catenin and COX-2 in a colitis-associated cancer experimental group, while the levels of IL-1β, TNF-α, TLR-4, and Myd88 were significantly decreased with tropisetron treatment^[157].

Cyclopentenone prostaglandin 15-deoxy-Δ 12,14-PGJ 2: Treatment of experimental colitis model rats with 15-deoxy-Δ 12,14-PGJ 2 (15d-PGJ2) resulted in significant attenuation of severity of colon damage, which was attributed to reduced iNOS and suppressed NF-κB-DNA binding in 15d-PGJ2 treated group^[158].

Glucosamine oligomers: Colitis animals treated with glucosamine oligomers have shown a significant reduction in the expression of iNOS and NF-κB, and prolongation of survival time^[159]. Oral administration of glucosamine oligomers inhibited inflammation in colonic mucosa by suppressing MPO activity in inflammatory cells, and by reducing NF-κB, COX-2, iNOS, and the serum levels of TNF-α and IL-6^[159].

8-hydroxydeoxy guanosine: 8-hydroxydeoxy guanosine (8-OHdG) is a product of ROS attacking guanine bases in DNA, which can bind thymidine rather than cytosine. Therefore, 8-OHdG is a biomarker of mutagenesis consequent to oxidative stress. It was shown that the administration of exogenous 8-OHdG can repress NF-κB signaling, pro-inflammatory cytokines, COX-2 and iNOS expression in stress-induced and inflammation-based GI tract conditions. Such outcomes might show a potential beneficial therapeutic effect^[160].

Macrophage migration inhibitory factor inhibitor: In RAW 264.7 cells, migration inhibitory factor (MIF) inhibitor significantly reduced inflammation by inhibiting MIF-induced NF-κB nuclear translocation and NO production, proposing a new strategy for colitis management^[161].

Telmisartan: Telmisartan administration diminished NF-κB p65 protein expression, and reduced the expression of iNOS and COX-2 in a colitis rat model^[162].

Amitriptyline: Amitriptyline is an antidepressant that is used to control the

psychosomatic symptoms of GI disorders. It was reported that amitriptyline inhibited the degradation of IkB, and the production of NO and TNF- α ^[163], suggesting a possible role for amitriptyline in colitis treatment.

Recombinant human IL-11: *In vitro* treatment of macrophages with recombinant human IL-11 (rhIL-11) caused a meaningful decrease in NF- κ B-DNA binding and the production of pro-inflammatory cytokines and NO. Co-administration of normal intestinal cells with rhIL-11 reduced cellular proliferation, representative of a possible function of rhIL-11 in treating colitis patients with IL-11^[164].

Non-NF- κ B dependent synthetic molecules

Herein, we address studies that evaluated the effect of synthetic compounds on NO production and colitis severity, regardless of the NF- κ B pathway.

NO intervention: Although the whole context of this review has been concentrated on the detrimental effect of the overproduction of NO in colitis progression, some studies indicated that a basal amount of NO, mainly produced by eNOS, is necessary for normal colon physiology. In animal models of colitis, the administration of nitrite or nitrate results in attenuation of colitis activity and damage, covering both preventive and therapeutic approaches^[28]. Considering the key role of NO in colon damage induced by colitis, one would think it is reasonable to develop a set of direct iNOS inhibitors to manage the condition. Despite such a straightforward idea, the iNOS inhibitors raised a contentious scientific argument, as a number of investigations reported no improvement, while some others have found promising results^[165,166]. For instance, Methylene blue which is a well-known NOS inhibitor was shown to reduce mucosal inflammation damage and decrease the expression of iNOS and MPO in colitis experimental models^[167]. The difference in eNOS antagonism affinity of antagonists used in each study was assumed to be the underlying reason for this inconsistency.

Nicotine: The positive effect of nicotine on UC, but not CD, has been known for quite a long time. However, data are not congruent regarding the correlation between NO and nicotine; some have noted a significant decrease in iNOS expression and NO production, while in some cases these effects were not observed. However, it has been accepted that nicotine is able to reduce the severity of colon inflammation in some settings^[168,169].

Anti-inflammatory drugs: As noted above, dexamethasone had positive effects on colitis mainly by reducing NF- κ B activity. Budesonide and Prednisolone, which are corticosteroids, attenuated inflammation and iNOS expression in UC cases^[170]. Celecoxib, Rofecoxib, and Nimesulide, which are non-steroidal COX-2 inhibitor anti-inflammatory drugs, have also significantly repressed iNOS activity and inflammatory damage in the colon^[171,172]. Sulfasalazine and Azathioprine did not affect NO production in colitis^[173].

Drugs with collateral anti-inflammatory effects: A broad list of chemical compounds and drugs has been investigated as NO inhibitors. Of note, Trimetazidine, Minocycline, N-Acetylcysteine, Pravastatin, Glutamine, Lactulose, Carvedilol, and Melatonin are all among the approved drugs for other medical conditions rather than inflammation, nonetheless, they have also been shown to possess anti-inflammatory and iNOS inhibitory effects, at least to some extent.

Trimetazidine: Trimetazidine is mainly used for angina pectoris and is considered to be a favorable drug for colitis treatment that reduces colon damage severity and NO production. The effect of Trimetazidine was correlated with the antioxidant properties of this drug^[174].

Minocycline: Apart from Minocycline's antibiotic properties, it has also been shown to regulate inflammation in some medical conditions. In colitis, Minocycline inhibited iNOS expression and reduced colon inflammation, damage and mortality^[175]. Although activation of the NF- κ B pathway by Minocycline is greatly supported by the literature, enhancement of NF- κ B in colonic tissue is still in doubt^[175].

Doxycycline: Another antibiotic, Doxycycline, has shown promising immunomodulatory properties. Doxycycline can ameliorate colitis and colon damage by decreasing the pro-inflammatory cytokine, IL-8 and NO generation, an effect which is even enhanced when it is concurrently administered with *Saccharomyces boulardii*^[176].

N-acetylcysteine: N-acetylcysteine (NAC) is a known antioxidant agent and has been shown to substantially reduce colon damage and NO production, particularly in

relatively higher doses^[177]. In a DSS-induced colitis model, NAC attenuated macroscopic and histopathologic colonic damage similar to 5-ASA treated mice. In addition, NAC reduced colonic MPO activity, ROS, TNF- α , and IL-1 β levels, while elevating paraoxonase/arylesterase 1 (PON1) activity, and GSH concentration. Overexpression of PON1 and scavenging of oxygen-derived free radicals might be the mechanisms underlying the protective effect of NAC in colitis treatment^[178].

Pravastatin: Pravastatin is a β -Hydroxy β -methylglutaryl-CoA (HMG-CoA) reductase inhibitor, able to ameliorate colitis severity and reduce colitis symptoms. Colitis model mice lacking eNOS have not shown this effect, suggesting that Pravastatin exerts its anti-inflammatory effects by upregulating eNOS expression rather than inhibiting iNOS^[179].

Lactulose: Lactulose is a well-known osmotic anti-constipation agent, but also reduces TNF- α and leukotriene B₄ production, as well as iNOS inhibition, mostly due to its probiotic properties, leading to *Lactobacilli* and *Bifidobacteria* overgrowth in the colon^[180].

Carvedilol: Carvedilol, a nonselective β -adrenoceptor antagonist with α 1-adrenoceptor antagonist activity, is also an antioxidant and anti-inflammatory agent. Carvedilol attenuated colon histopathological damage and iNOS expression, and reduced TNF- α , IL-1 β , IL-6 and PGE2 levels^[181].

Melatonin: Melatonin administration in colitis models improved the disease symptoms, and decreased the expression of iNOS, COX-2 and MPO^[182,183]. There have been some efforts to develop colon-specific sodium alginate gels containing melatonin, to confirm melatonin associated anti-inflammatory effects^[182]. The fact that melatonin is a sleep-related neurohormone might propose a relationship between sleep patterns and colitis pathogenesis, which can be a topic of future studies.

Miscellaneous compounds

Soluble guanylate cyclase inhibitors: Colitis is associated with a reduced soluble guanylate cyclase (SGC) sensitivity, hence, a reduced colonic response to nitrergic stimuli. This finding puts forward the idea that inhibition of SGC might enhance colon protection in colitis. In contrast, several studies claimed that the pharmacological inhibition of SGC does not exert any protective effects in colitis^[184].

Calpain inhibitor I: Calpain is a family of calcium-dependent proteases, and although their physiologic functions are poorly understood, they are thought to be of importance in cellular functions such as cell mobility and apoptosis^[185]. Calpain inhibition has been found to cause a significant reduction in iNOS expression in colitis animals^[186].

IL-4: Transfection of colon with IL-4-gene-carrying adenovirus vectors has successfully increased IL-4 concentration, and significantly reduced the expression of INF- γ , MPO and iNOS^[187].

TNF- α Convertase (TACE/ADAM17) inhibition: BB1101, a TACE/ADAM17 inhibitor has shown a promising suppressive effect on iNOS expression and TNF- α release in the colon of IBD animals, leading to a significant anti-inflammatory effect^[188].

α -Melanocyte-stimulating hormone: In colitis settings, administration of α -Melanocyte-stimulating hormone, a melanogenesis stimulator, can significantly affect NO production, modulating inflammation and providing protective benefits in the colon^[189].

Ursodeoxycholate: Ursodeoxycholate, a bile acid, has successfully protected the colon against LPS-induced colitis in rats, mainly by hampering iNOS activity^[190].

(Arginine-glycine-aspartic acid) RGD motif: It has been proposed that integrins have great importance in colitis pathogenesis and their dysfunction can cause an inflamed colon due to leukocyte recruitment. As an integrin motif, administration of RGD to the colon, using silk functionalized particles, resulted in a significant decrease in iNOS expression^[191].

3,3'-diindolylmethane: 3,3'-diindolylmethane, a cruciferous family of vegetables derived molecule has been shown to inhibit iNOS and COX-2 expression^[192]. The underlying mechanism is not fully understood.

GL-V9: This compound is a synthetic flavonoid, capable of inhibiting inflammatory

cells infiltration and decreasing MPO and iNOS activities^[193]. Furthermore, GL-V9 decreased pro-inflammatory cytokines and ROS production, increased antioxidant defenses in mouse macrophage RAW264.7 cells; mainly by promoting Trx-1 expression. It has been demonstrated that GL-V9 decreased oxidative stress by up-regulating Trx-1 *via* activation of the AMPK/FOXO3a pathway, suggesting that GL-V9 might be a potential choice for IBD^[193].

Propionyl-L-carnitine: Propionyl-L-carnitine, an antioxidant molecule, inhibited oxidative stress-induced CAM expression, thus, reducing leukocyte infiltration in the colon, which then led to a significant reduction in iNOS expression^[194].

Tetrahydrobiopterin: The enzyme cofactor tetrahydrobiopterin is a fundamental part of biogenic amine synthesis, lipid metabolism and redox coupling of NOS. An oral suspension of tetrahydrobiopterin was shown to reduce iNOS activity and increase regulatory T cells in the colon environment, leading to reduced colon inflammation, shrinkage and swelling^[195].

CONCLUSION

It has been shown that NO has a significant role in the pathogenesis and treatment of IBD. In this paper, pharmacological interventions that affect IBD, especially those modulating the NO pathways, were reviewed in two distinct categories: natural agents *i.e.*, flavonoids can decrease NO production and iNOS expression, leading to therapeutic effects comparable with Mesalazine in IBD. NF- κ B and JAK/STAT are the major pathways involved in this process. Activation of PPAR γ , inhibition of iNOS, and suppression of TLR-4 upregulation; in addition to the secretion of inflammatory cytokines are considered to be the main therapeutic mechanisms of flavonoids in this regard. This review indicates that other polyphenol compounds could also be beneficial, mainly due to iNOS modulation and NF- κ B suppression. Interestingly, a number of these compounds could even upregulate eNOS, which is necessary for normal colon physiology. Probiotics and prebiotics can also alter the intestinal microbiome and have the ability to prevent or reduce inflammation in IBD. Previous studies indicated that pro- and pre-biotics reduce NO production and suppress iNOS activity through different mechanisms such as suppressing the I κ B/NF- κ B pathway, IL-10 secretion, dendritic cells-induced IL-12 secretion, and modulating the expression of iNOS and TLR 4. It has been suggested that dairy products have similar properties, seemingly by altering the colonic bacterial population. Fatty acids such as PUFAs can also improve IBD by modulating the production of eicosanoids, COX-2, PPAR- γ , and NF- κ B, and exhibiting inhibitory effects on iNOS.

Sulfasalazine and Azathioprine are fundamental anti-inflammatory and immunomodulatory drugs for IBD treatment, but have no effect on NO production in colitis. Synthetic compounds could also be effective treatments for IBD, of which some (*i.e.*, Dexamethasone, Pioglitazone, Tropisetron) can act through the NO and NF- κ B signaling pathways. Other therapeutic compounds could regulate NO, independent of NF- κ B. For instance, nicotine; anti-inflammatory agents (*i.e.*, Prednisolone and Celecoxib); β -adrenoceptor antagonist with α 1-adrenoceptor antagonist activity (*i.e.*, Carvedilol); antioxidants (*i.e.*, N-Acetylcysteine); and specific iNOS inhibitors (*i.e.*, Methylene blue) are able to attenuate iNOS expression and NO production, directly or by mechanisms other than the NF- κ B signaling pathway.

It is important to mention that the IBD inhibitory effects of phytochemicals or their combination with conventional therapeutics are principally implicated due to their ability to modulate the main pathophysiological factors of IBD development; inflammatory cytokines (*i.e.*, IL-6, IL-12) production. Although, such treatments are affordable, they can alleviate the pain and inhibit inflammation in IBD patients, however, the major drawback of natural compounds is their mode of action, and their limited bioavailability at the site of inflammation. In comparison, the antibody based treatments such as anti-TNF biologics (*i.e.*, Infliximab, Adalimumab or Etanercept) have more specificity, can lower cytokine production, inhibit inflammatory cell recruitment, and induce cell death of inflammatory cells, while representing less efficacy, as a significant percentage of patients do not respond to anti-TNF treatment. Furthermore, such therapeutics are expensive and showed some adverse effects such as increased risk of infection and malignancy or may cause *de novo* autoimmune diseases^[196-198]. Overall, this review highlights the importance of NO in the pathogenesis and treatment of IBD. It seems the (co)administration of natural or chemical NO-regulating compounds might be favorable for patients suffering from IBD. Further investigations and well-designed trials are worth consideration.

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