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EDITED BY
Rajeev K. Tyagi,
Institute of Microbial Technology (CSIR), India

REVIEWED BY
Chengxin Sun,
Zunyi Medical University, China
Joshua R. Sacher,
Photys Therapeutics, United States

*CORRESPONDENCE
Niloofar Deravi,
niloofarderavi@sbmu.ac.ir

†These authors have contributed equally to this work

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Zingiber officinale (Ginger) as a treatment for inflammatory bowel disease: A review of current literature

Fatemeh Sadeghi Poor Ranjbar[1†], Fatemeh Mohammadyari[2†], Atharzahra Omidvar[3], Farhad Nikzad[3], Nooria Doozandeh Nargesi[2], Majid Varmazyar[4], Soroush Dehghankar[5], Fatemeh Vosoughian[6], Sepehr Olangian-Tehrani[5], Sepehr Nanbakhsh[5], Tina Mansourian[6], Niloofar Deravi[6*], Zohreh Tutunchian[7], Mehrnaz Salahi[7], Mohadeseh Poudineh[8] and Hani Ghayyem[9]

[1]Student Research Committee, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran, [2]School of Medicine, Guilan University of Medical Sciences, Rasht, Iran, [3]Student Research Committee, International Campus, Shahid Sadoughi University of Medical Sciences, Yazd, Iran, [4]Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran, [5]Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran, [6]Student Research Committee, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [7]Student Research Committee, School of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran, [8]School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran, [9]School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Inflammatory bowel disease (IBD) is a term used for a variety of conditions involving persistent inflammation of the digestive system. Ulcerative colitis (UC) and Crohn's disease (CD) are examples of IBD. There were some treatments like Amino salicylates, glucocorticoids, immunosuppressants, antibiotics, and surgery which have been used for treating IBD. However, the short and long-term disabling adverse effects, like nausea, pancreatitis, elevated liver enzymes, allergic reactions, and other life-threatening complications remain a significant clinical problem. On the other hand, herbal medicine, believed to be safer, cheaper, and easily available, has gained popularity for treating IBD. Nowadays, Ginger, the Rizhome of *Z. officinale* from the Zingiberaceae family, one of the most commonly used fresh spices and herbs, has been proposed as a potential option for IBD treatment. According to upper issues,

Abbreviations: APC, adenomatous polyposis coli; AUC, acute ulcerative colitis; AZ-SFE, supercritical fluid extract of *Angelica sinensis* and *Z. officinale* roscoe; CD, Crohn's disease; Con.A, concanavalin A; COX-2, cyclooxygenase-2; DSS, dextran sulfate sodium; GDNP, ginger loaded nanoparticles; GDNPs 1, ginger derived nanoparticles (8/30%); GDNPs 2, ginger derived nanoparticles (30/45%); GDNV, ginger-derived nano vectors; GE, ginger extract; GVDLs, ginger-derived lipid vehicles; IL-1β, interleukin-1β; iNOS, inducible nitric oxide synthase; Lcn-2, lipocalin-2; LPS, lipopolysaccharide; MAPK, mitogen activated protein kinase; MDA, malondialdehyde; MOR, *Moringa oleifera*; MPO, myeloperoxidase; MTT, [3-(4,5-dimethythiazol-2-yl)-2,5-diphenyl tetrazolium bromide]; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NIM, nimesulide: a selective COX-2 inhibitor; NO, nitrogen monoxide; PCO, protein carbonyl; TNBS, trinitrobenzene sulfonic acid; TNF-α, tumor necrosis factor; UC, ulcerative colitis; ZER, zerumbone: a sesquiterpenoid with very large amounts detected in rhizomes.

IBD treatment has become one of the society's concerns. So, this review aims to summarize the data on the yin and yang of ginger use in IBD treatment.

KEYWORDS

Z. officinale, ginger, ulcerative colitis, inflammatory bowel disease, natural compound

Introduction

CD and UC (examples of inflammatory bowel disorders) are relapsing, chronic, idiopathic, and remitting conditions of the gastrointestinal tract with an increasing incidence worldwide for which existing therapies are mostly limited by severe side effects (Chan and Giovannucci 2010; Terzić, Grivennikov et al., 2010; Sussman, Santaolalla et al., 2012). Typical clinical signs and symptoms of IBD, such as diarrhea, abdominal pain, hematochezia, as well as clinical signs of bleeding and intestinal obstruction, relying on the location of the disease, which may significantly reduce the patient's quality of life. Despite the fact that the etiology of IBD is not well understood, both environmental factors and genetics are known as contributive risks (Fiocchi 1998). Cytokines, reactive oxygen metabolites, and eicosanoids are all inflammatory mediators with a role in the progression of the disease (Seo, Takata et al., 1995; Loguercio, D'Argenio et al., 1996; Carty, De Brabander et al., 2000). Amino salicylates, glucocorticoids, immunosuppressants, antibiotics, and surgery, in some cases, have been used for the treatment of IBD. However, the short and long-term disabling adverse effects like, nausea, pancreatitis, elevated liver enzymes, allergic reactions, and other life-threatening complications remain a significant clinical problem (Navaneethan and Lashner 2013). Furthermore, most of the medicines listed above need regular high-dose administration to achieve significant clinical effectiveness (Ensign et al., 2012; Moriasi et al., 2012; Wang and DuBois 2013; Dulai et al., 2014; Xiao et al., 2014; Zhang et al., 2015). In recent years, herbal therapies have shown beneficial effects in IBD patients (Ng et al., 2013). Nanoparticles have been used in treating IBD patients and in addition, it can be used to deliver low doses of medicines to special tissues and cell types while also reducing systemic adverse effects (Laroui et al., 2010; Laroui et al., 2011; Xiao et al., 2013; Morton et al., 2014; Xiao et al., 2014; Araújo et al., 2015; Han et al., 2015; Hansen et al., 2015; Ramishetti et al., 2015; Tang et al., 2015; Xiao et al., 2015; Xing et al., 2015).

Ginger, the Rizhome of *Z. officinale* from the Zingiberaceae family, is one of the most commonly used fresh spices and herbs, containing many active phenolic components such as Shogaol, Gingerol, and Zingerone (Algieri et al., 2015). These components have anti-inflammatory, antioxidative, and immunomodulatory properties (Mozaffari-Khosravi et al., 2016). Ginger has traditionally been used as a remedy for gingivitis, rheumatism, stroke, asthma, and diabetes (Afzal et al., 2001). Ginger has also been known as a "broad-spectrum anti-emetic" cause of its prevention of nausea resulting from postoperative courses, pregnancy, and motion sickness (Ali et al., 2008). Also, the efficacy of ginger as a remedy to improve IBD has been reported in many studies (Ensign et al., 2012; Ng et al., 2013; Xiao et al., 2014). Therefore, this review aims to summarize the results of studies on the potential efficacy or possible side effects of ginger in the IBD treatment.

Methods

We conducted a comprehensive search in online databases (PubMed, Google Scholar, Scopus, and Science Direct) published up to September 2021, to find studies investigating the effect of ginger in the treatment of IBD. No language limit was exerted. Our keywords included Ginger, *Z. officinale*, Gingerol, Zingerone, Inflammatory bowel diseases (IBDs), Ulcerative colitis, and Crohn's disease.

Due to the importance of ginger and current investigations, we divided these studies into two parts: *in vivo* and *in vitro* studies.

In vivo studies

The efficacy of ginger has been shown in several *in vivo* and *in vitro* studies (Tables 1, 2). Studies demonstrated that T cells have a significant function in the immunological mechanisms of IBD. These data were concluded from genome-wide association studies, animal models of IBD, and some clinical trials. Inflammation is induced by Th1/Th17 cells that produce IFN-γ and IL-17; while TGF-β and IL-10 produced by Th2 have anti-inflammatory functions, for example, IL-10 inhibits pro-inflammatory cytokine expression by adaptive cells using STAT3-dependent signaling. Moreover, they have claimed that IL-17A enforces epithelial barrier function, so an inflammatory cytokine will be induced using an NF-κB dependent signaling (Gálvez 2014; Chen and Sundrud 2016).

In 2018, Chen et al. (2018) investigated the effect of the volatile of *Amomum villosum* (VOAV), a herbaceous plant in the ginger family, on the immunological function of T cells in IBD rats. They discovered that VOAV therapy reduced IL-17 and IFN- levels while increasing TGF- and IL-10 levels. Therefore, VOAV therapy reduced the level of pro-inflammatory cytokines and clearly repressed intestinal inflammation in IBD rats. These results were

TABLE 1 The characteristics of the included *in vivo* studies on the effect of ginger on IBD.

Author/ year	*In vivo* study design	Dose	Duration	Findings	Reference
Guo et al., 2021	32 Male BALB/c mice (weighing 18–22 g) divided into four groups with dextran sulfate sodium (DSS) induced colitis	1) The control group was fed with standard rodent food and water without any other treatment; 2) The model group provided free access to 2.5% DSS, and orally administered normal saline at 100 μl/20 g daily; 3) was provided free access to 2.5% DSS and orally administered SASP at 400 mg/kg daily; 4) Provided free access to 2.5% DSS and orally administered Ginger at 500 mg/kg daily	Acclimatization for 3 days testing for 7 days	Mice administered ginger and SASP showed a lower weight loss than the model group. The disease activity index (DAI) of mice administered Ginger and SASP was also decreased significantly. Colon length shortening was less in ginger- and SASP-treated mice than in the model group mice. The spleen index of the Ginger- and SASP-treated mice was significantly lower than the model group mice Overall ginger inhibited colitis progression, alleviated colon injury, and regulated the fecal microbiome	Guo et al., 2021
EL-Abhar et al., 2008	48 Male Wistar rats with acetic acid-induced UC	Gp1.2: Vehicle Gp3.4.5: GE 100, 200, 400 mg/kg/d, respectively Gp6: Sulfasalazine	3 days before and 7 days after induction	MDA and PCO improvement with GE was comparable with high doses of sulfasalazine. Ginger had an effect against acetic acid-induced UC through its anti-oxidants and anti-inflammatory properties	El-Abhar et al. (2008)
Ajayi et al., 2008	36 adult male BALB/c mice with DSS-induced chronic UC	Gp1: Corn oil (control) GP2: Normal mice chow and DSS Gp3: 100 mg/kg/d 6-Gingerol and DSS Gp4: Sulfasalazine and DSS Gp5: 6-Gingerol 100 mg/kg/d Gp6: Sulfasalazine	63 days	In UC cases, 6-Gingerol Ameliorates: phenotypic clinical features, oxide-inflammatory stress indices, histopathological damages, pro-inflammatory cytokines and chemokines, NF-kB (P65), p38, and iNOS expressions, COX-2 and, catenin while it increases APC expression, inhibits aberrant crypt foci formation	Ajayi et al. (2018)
Zhang et al. (2017)	3 Female FVB mice	GDLVs-siRNA complex Orally administrated Twice	Administrations 12 h apart	Orally administered siRNA-CD98/ GDLVs reduced the expression of CD98 in ileum and colon but did not affect duodenum or jejunum	Zhang et al., 2017
Kim et al. (2018)	40 female BALB/c mice in five groups (n = 8) with 5% DSS-induced colitis	Gp1: Water GP2: DSS Gp3: DSS +100 mg/kg ginger orally, once a day Gp4: DSS +300 mg/kg ginger orally, once a day Gp5: DSS +500 mg/kg ginger orally, once a day	21 days	Improved symptoms of DSS-induce colitis: inhibited shortening of colon, increased body weight, attenuated and reduced the MPO activity and pro-inflammatory cytokines and mRNA expression but enhanced the mRNA expression of tight junction proteins	Kim et al. (2020)
Abdel Gawad et al. (2007)	48 Male Sprague-Dawley rats divided into six groups (n = 8) with acetic acid-induced UC	Gp1: Saline Gp2: Positive control Gp3: 100 mg/kg GE Gp4: 200 mg/kg GE Gp5: 400 mg/kg GE	Three consecutive days before intra-rectal acetic acid administration and 7 days after the induction = 10 days	Reduced the lesions scores macroscopic colonic damage and the histopathological changes- by having a protective effect against acetic acid, damage to the epithelium	Abdel Gawad et al. (2007)

(Continued on following page)

TABLE 1 (*Continued*) The characteristics of the included *in vivo* studies on the effect of ginger on IBD.

Author/ year	*In vivo* study design	Dose	Duration	Findings	Reference
El-masry et al., 2016	40 BALB/c mice divided into five groups ($n = 8$) with colitis	Gp1: Filtered water Gp2: 5% DSS Gp3: 200 mg/kg MOR orally Gp4: 100 mg/kg/d ginger orally Gp5: 200 mg/kg/d MOR and 100 mg/kg/d ginger orally	10 days	increased anti-inflammatory, improved immune system efficiency, effected as an anti-oxidant	El-masry et al. (2016)
Minaiyan et al. (2007)	66 male Wistar rats divided into 11 groups ($n = 6$) with acute colitis	Gp1,2,3,4: Normal saline Gp5,6,7: 150–700 mg/kg Ginger hydro alcoholic extract, orally Gp8,9: 350–700 mg/kg Ginger hydro alcoholic extract Gp10,11: Hydrocortisone acetate or prednisolone	5 days Gp5, 6: The final dosage was given 2 h before the colitis induction Gp8,9: 15 and 2 h before colitis induction	Effected anti-inflammatory, effected as an anti-oxidant, modulated the immune system	Minaiyan et al. (2007)
Rashidian et al	Six male Wistar rats with acid-induced colitis	Ginger volatile oil at dosages of 100–400 mg/kg Normal control: Saline 2 ml/kg Model control: Saline 2 ml/kg 100 mg/kg volatile oil in Group 1 Group 2 (volatile oil): 200 mg/kg 400 mg/kg volatile oil in Group 3 Prednisolone group: 4 mg/kg prednisolone	6 days	Ginger volatile oil with all doses lowered colon weight, length and ratio considerably, and the results were comparable to the reference treatments.Higher oral doses of volatile oil (200 and 400 mg/kg) lowered ulcer severity, ulcer area and ulcer index markedly.The dose of 400 mg/kg of volatile oil was advantageous to considerably lower inflammation severity and inflammation extent compared to the control group	Rashidian et al. (2014)
Murakami et al	75 Female ICR mice with dextran sodium sulfate-induced colitis	Control group (1): Tap water Group 2: 5% DSS in tap water Group 3: 0.1% ZER (a) Group4: 0.1% NIM (b) Group 5: 0.1% ZER plus 0.1% NIM	1 month	Oral feeding of ZER attenuated DSS(c) -induced colitis, while NIM controlled the histological alterations generated by DSS without changing inflammatory biomarkers. However, their therapy in combination was most effective for lowering these indicators. The data show that ZER is a novel dietary component for minimizing experimental UC.	Murakami et al. (2003)
Abd Allah et al	36 Male Wistar Albino rats with acetic acid-induced colitis	1. Normal control group: 2 ml distilled water for 5 days 2. Ginger control group: 2 ml distilled water + 400 mg/kg ginger for 5 days 3. Colitis-24 h group: 2 ml distilled water for 5 days + AA for 24 h 4. Ginger-preventive group: 400 mg/kg ginger for 5 days + AA for 24 h	5 days	Ginger therapy ameliorated the effects of AA(e)-induced colitis by reducing colon weight-to-length ratio, macroscopic and microscopic scores These effects were further corroborated by the down-regulation of NF-kB and decreased colonic IL-10, TP, TNF- α, and serum 5-HT levels Furthermore, there were significant positive relationships between serum 5-HT and macroscopic, microscopic, immunoreactivity scores and colonic TNF-α levels In conclusion, Ginger ameliorated AA-induced colitis not only through its anti-inflammatory and antioxidant features but also *via* the lowering of 5-HT, which may	Abd Allah et al. (2016)

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TABLE 1 (*Continued*) The characteristics of the included *in vivo* studies on the effect of ginger on IBD.

Author/ year	*In vivo* study design	Dose	Duration	Findings	Reference
				contribute to the down-regulation of NF-kB-dependent TNF- α production and the reduction of lipid peroxidation and tissue damage	
		5. Colitis-5-days group: AA for 24 h + 2 ml distilled water for 5 days		In addition, ginger's therapeutic influence was greater than its preventive effect	
		6. Ginger-treated group: AA for 24 h + 400 mg/kg ginger for 5 days			
Zhang et al	FVB/NJ mice with dextran sodium sulfate-induced colitis	On animals Control group: Plain water DSS control: DSS Group 3: NPs-PEG-FA/6-shogaol Group 4: Free 6-shogaol	1 h–14 days	*In vivo*, oral administration with NPs-PEG-FA/6-shogaol dramatically decreased colitis symptoms and expedited colitis wound healing in DSS-treated mice *via* modulating the expression levels of pro-inflammatory (TNF-α, IL-6, IL-1β, and iNOS) and anti-inflammatory (Nrf-2 and HO-1) proteins	Zhang et al. (2018)
Liu et al., 2019	30 male Sprague Dawley rats with single-dose TNBS-induced colitis	*In vivo* Gp1: Control Gp2: TNBS Gp3: TNBS/mesalazine Gp4: TNBS/AZ-SFE (30 mg/kg) GP5: TNBS/AZ-SFE (60 mg/kg)	*In vivo*: Once a day for seven consecutive days from the day after induction	*In vivo*: AZ-SFE effectively attenuated disease activity, colonic shortening, macroscopic and histological damage of TNBS-treated rats with decreased oxidative stress, suppressed inflammatory cytokines and altered hepcidin and serum iron	Liu et al. (2019)
Hsiang et al., 2013	24 female BALB/c mice with TNBS-induced colitis	Gp1: Mock, given ethanol GP2: TNBS, given TNBS Gp3: TNBS/ginger, given mixtures containing TNBS and ginger (0.1–100 mg/kg) Gp4: TNBS/zingerone, given mixtures containing TNBS and zingerone (0.1–100 mg/kg)	7 days	Ginger and zingerone ameliorated TNBS-induced colonic injury and significantly downregulated cytokine-associated pathways which upregulated *via* NBS induced colitis. Additionally, (NF-κB) and (IL-1β) were essential molecules involved in the expression of ginger- and zingerone-affected genes and ginger and zingerone reduced TNBS-induced NF-κB activation and lowered the TNBS-increased NF-κB and IL-1β protein levels in the colon	Hsiang et al. (2013)
Shanshan Guo et al. (2021)	32 male BALB/C mice with UC	Divided in four groups Group1: standard food and water Group2: 2.5% DSS + 100 μL/20 normal saline orally, once a day Group3: 2.5% DSS + 400 mg/kg SASP orally, once a day Group4: 2.5% DSS + 500 mg/kg ginger orally, once a day	7 days	Decreased body weight and reduced disease activity, inhibited shortening of colon, decreased spleen index decreased the mRNA expression levels of these inflammatory cytokines and reduced severe intestinal mucosa injury and inflammatory cells	Guo et al. (2021)
Eidnahed Soliman 2021	20 rats	Divided into four groups Group1: control Group2: AUC Group3: AUC received 2.5 mg GE Group4:2.5 mg superparamagnetic@ silver nanoparticles GDNP	NAN	GDNP was more effective in compare with GE. Improved signs, reduced apoptosis and effective repair of AUC more significantly	Al Badawi, Waly et al. (2021)

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TABLE 1 (*Continued*) The characteristics of the included *in vivo* studies on the effect of ginger on IBD.

Author/ year	*In vivo* study design	Dose	Duration	Findings	Reference
Sung et al., 2022	20 female mice 6–8 weeks with 2% DSS for 7 days in a row to induce mild colitis in 15 mice	Group 1: Healthy control Group 2: DSS + PBS Group 3: DSS + blank nLNPs Group 4: DSS + IL-22/nLNPs The dosage of IL22/nLNPs was 200 μg/kg (or 4 μg/mouse) and dosed volume was 200 μl for each mouse	7 days	mice fed with IL-22/nLNPs experienced an accelerated healing process, as indicated by the recovery of more body weight and colon length as well as reduction of the histological index, colonic MPO activity, fecal lipocalin concentration, and mRNA expression levels of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β)nLNPs is an excellent mRNA delivery platform for treating ulcerative colitis	Sung et al. (2022)

also supported in an *in vivo* part of a study by Zhang et al. In which they studied a particular population of nanoparticles that were derived from edible ginger (GDNPs 2) and analyzed their IBD targeting following oral administration. These particles contain high levels of bioactive elements of ginger like 6-gingerol and 6-shogaol. Using different mouse models, they claimed that oral use of GDNPs 2 reduced the pro-inflammatory cytokines like IL-10 and IL-22 (Zhang et al., 2016). Guo et al. (2021) evaluated the effect of ginger on improving symptoms of UC using a DSS-induced mice colitis model. Ginger inhibited colon shortening decreased INOs, IL-6, and the mRNA expression levels of inflammatory cytokines, Hematoxylin, and Eosin (H&E) staining of the colon tissues. Less severe intestinal mucosa injury and regulated the fecal microbiome compared to the control group. Reduced lesions and histopathological changes in the colon subsequent to the use of the ginger extract in rats with acetic acid-induced UC have also been reported (Abdel Gawad et al., 2007). Hsiang et al. (2013), for the first time, demonstrated that ginger and its constituent zingerone could improve TNBS-induced colitis in mice *via* modulation of IL-1β signaling pathway and NF-κB activity. Ginger plus zingerone therapy reduced the number of brown cells in the colon. They also substantially regulated numerous cytokine expressions, such as IL-6, IL-1β, interferon-c, IL-17, and tumor necrosis factor (TNF-α). Toll-like receptors (TLRs) were increased by TNBS, which resulted

TABLE 2 The characteristics of the included *in vitro* studies on the effect of ginger on IBD.

Author/ year	*In vitro* study design	Dose	Duration	Findings	Reference
Zhang et al. (2017)	Caco-2BBE, RAW264.7, Colon-26 cells	GDNV (5,10,20,50,100, and 200 μM)	24 h incubation	GVDLs: are biocompatible and do not affect the integrity of intestinal barrier function and do not induce apoptosis in RAW 264.7 & colon-26 cells. SiRNA-CD98/GDLVs can decrease CD98 expression	Zhang et al. (2017)
Zhang et al	Raw 264.7 macrophage and colon-26 cells	In culture:Ginger active compound 6-shogaol loaded NPs-PEG-FA nanoparticles (2mg/mL)	1 h to 14 days	Subsequent cellular uptake tests indicated that NPs-PEG-FA could undergo effective receptor-mediated uptake by colon-26 cells and activated Raw 264.7 macrophage cells	Zhang et al., 2018
Liu et al., 2019	1.normal RAW264.7 cells	*In vitro*:1.Gp1: VehicleGp2: AZ-SFE (2.5–160 μM) Gp3: ligustilide Gp4: 6-gingerol (2.5–160 μM)	*In vitro*: 1. 24 h incubation	*In vitro*	Liu et al. (2019)
	2.LPS-induced RAW264.7 cells	2. Gp1: blank control Gp2: LPS Gp3: LPS/AZ-SFE (0.625–20 μg/ml) Gp4: LPS/combination of Ligustilide and 6-gingerol (0.05–164 μg/ml)	2. 1 h pretreatment with AZ-SFE or a combination of ligustilide and 6-gingerol and then 24 h stimulation with LPS	Not only did AZ-SFE dramatically reduce the formation of NO in LPS-stimulated macrophages, but also stopped the proliferation of Con.A-induced splenocytes with suppression of the Th1 immune response	
	3.splenocytes	3. GP1: blank controlGP2: Con.A Gp3: Con.A/AZ-SFE (5–20 μg/ml)	3. 24 h incubation		

TABLE 3 The characteristics of the included human studies on the effect of ginger in IBD.

Author/ year	Human studies design	Dose	Duration	Findings	Reference
Nikklah-Baelaghi et al., 2019	46 patients with active UC	500 mg/d dried ginger powder in four capsules	6 weeks	ginger reduced serum MDA factor and TNF-α levels No important changes in inflammatory factors and quality of life Usage of 2 g of dried ginger root powder for 6 weeks decreased oxidative stress in cases with mild to modest UC	Nikkhah-Bodaghi et al. (2019)
Hashemi 2020	45 patients with mild to moderate UC randomly divided into two groups	2,000 mg/day of ginger powder in 4 capsules or placebo	12 weeks	The quality of life, Serum MDA, Serum TNF-α levels and level of hs-CRP was increased considerably subsequent to ginger use in cases with UC.	Abbas (2020)
Jun et al., 2015	60 patients with UC of spleen-kidney yang deficiency type	Group1: Live combined *Bifidobacterium*, *Lactobacillus,* and *Enterococcus* capsules, orally Group2: Live mixed *Bifidobacterium*, *Lactobacillus,* and *Enterococcus* pills, and had acupuncture and umbilical ring point ginger-partition moxibustion simultaneously	4 weeks	The serum TNF-α and IL-8 levels were lowered in both groups. Acupuncture coupled with umbilical ring point ginger-partition moxibustion is effective and safe for the treatment of UC of spleen-kidney yang deficient type	Jun et al. (2015)

Abbreviations: MDA, malondialdehyde; UC, ulcerative colitis; TNF-α, tumor necrosis factor; Crp, C-Reactive Protein; IL-8, interleukin-8.

in the activation of inflammation-related pathways and the development of intestinal inflammation, while ginger and zingerone inhibited TLR signaling and alleviated TNBS-induced colitis in mice.

In 2014, Rashidian et al. (2014) realized that volatile ginger oil could significantly relieve colitis symptoms. The results showed that volatile ginger oil decreased the inflammation severity, inflammation extent, and crypt damage induced by acetic acid and involvement percentage in a dose-dependent manner. The reference drug used in their study was oral prednisolone, and it was used to portray the effectiveness of the test substance. They assumed that pretreatment for 5 days with this drug enhanced the absorption and systemic availability of the active drugs. The same results were found using a medium and high doses of volatile ginger oil. Their results indicate that ginger may be advantageous in the treatment of colon mucosal damage caused by IBD due to its anti-lipo per oxidative and anti-oxidant actions. These properties originate from its ability to scavenge free radicals and protect cell membranes from oxidants, and overall its anti-oxidant value Ajayi et al. (2018) showed that 6-Gingerol could Ameliorate phenotypic clinical features of UC, such as rectal bleeding and diarrhea, and substantially minimize the rate of reduction in body weight, colon length, and colon weight in mice, oxido-inflammatory stress indices level [such as MDA levels, MPO activity and NO concentration (Owumi et al., 2020), pro-inflammatory cytokines, and chemokines] which have an established role in the growth of UC (Landskron et al., 2014). Ginger could also decrease the expression of iNOS, P65, p38, and NF- kB, which catalyze the production of NO. Reduced histopathological damages were also reported to decrease colonic neutrophil infiltration and mucosal ulcerations (Morris et al., 2003).

In vitro studies

There are many *in vitro* studies that confirm the effect of ginger in the treatment of inflammatory bowel disease. In addition to the previous studies, in 2017, Zhang et al. (2017) used ginger-derived nano lipids loaded with siRNA as a new path for siRNA drug delivery that could have fewer side effects for UC treatment in both *in vitro* and *in vivo* studies. The *in vitro* part was done on Caco-2BBE, RAW264.7, and Colon-26 cells, which were incubated with Ginger-derived nano vectors (GDNV). The result showed that Ginger-derived lipid vehicles (GVDLs) are biocompatible and have fewer effects on the viabilities of cell lines compared with Lipid nanoparticles (currently the favored vehicle for therapeutic siRNA delivery that causes cell stress, inflammation, and apoptosis). In addition, siRNA-CD98/GDLVs can decrease CD98 expression. Also, their results indicated that GDLVs could be developed as a nontoxic siRNA-delivery vehicle. GDLVs/siRNA-FITC were also taken up by cells by high efficacy, which means it can be used as a siRNA-delivery vehicle without using toxic transfection reagents (like Lipofectamine). The results suggest that GDLVs/siRNA-FITC has the potential to shift the current paradigm of siRNA delivery away from artificially synthesized

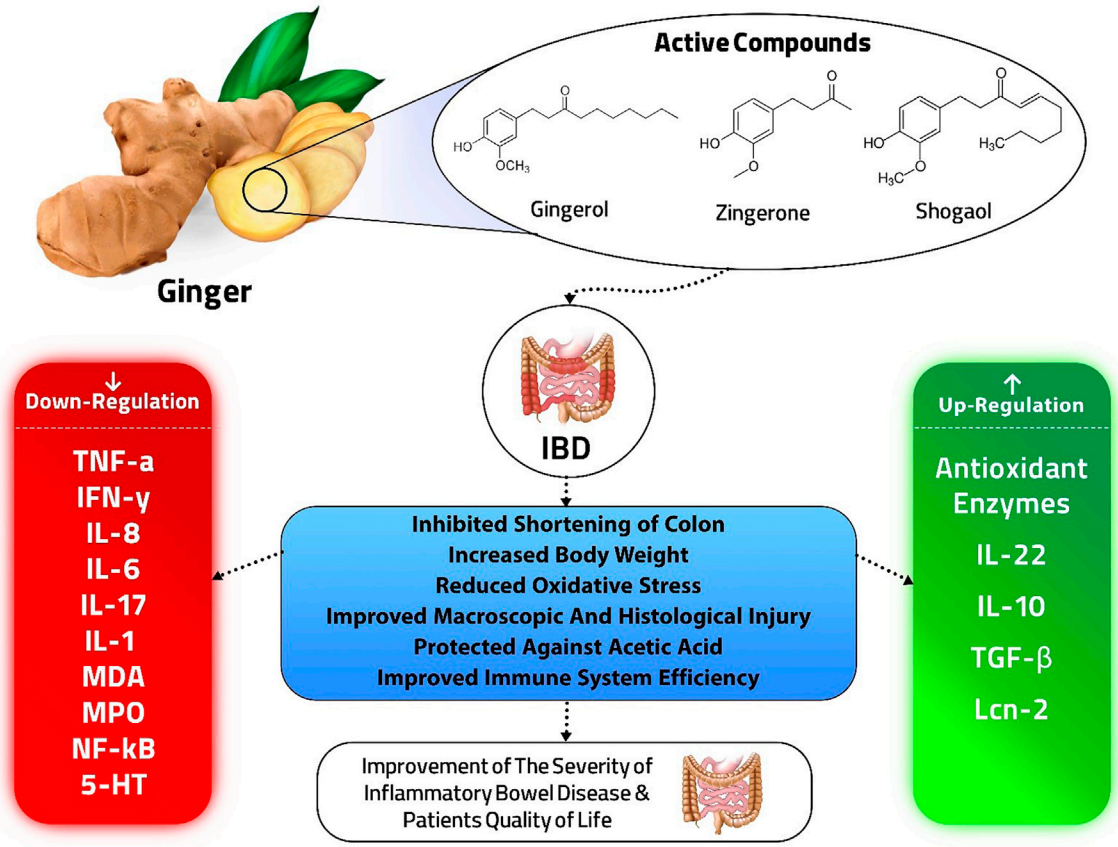

FIGURE 1
Underlying mechanisms of ginger in inflammatory bowel disease.

nanoparticles toward the use of nature-derived nano vehicles from edible plants.

Liu et al. (2019) did research about the anti-inflammatory characteristics of AZ-SFE *in vitro* by determining NO production on lipopolysaccharide (LPS)-induced RAW264.7 cells. LPS-induced RAW264.7 macrophages are typically used to assess the anti-inflammatory influence *in vitro*. The *in vitro* study augmented the investigation of the anti-colitis activity of AZ-SFE in the TNBS-induced rat model. They concluded that the following *in vitro* study showed the potential of AZ-SFE for mitigating colitis by cutting down the oxidative stress, inhibiting inflammatory mediators, impeding the Th1 immune response, and managing iron homeostasis. As a result, AZ-SFE derived from traditional Chinese herbs could be a promising supplement for recent IBD therapy, and the precise mechanism requires more investigation.

Oral drug delivery is the most appealing pathway for UC treatment, because it has many benefits. Adaptable Single-step surface-functionalizing method was used by Zhang et al. (2018) to prepare PLGA/PLA-PEG-FA nanoparticles loaded with the active ginger compound, 6-shogaol (NPs-PEG-FA/6-shogaol). They utilized both *in vitro* and *in vivo* models. The result indicated that NPs-PEG-FA showed great biocompatibility both *in vitro* and *in vivo*. Subsequent cellular uptake experiments exhibited that NPs-PEG-FA could undergo effective receptor-mediated uptake by colon-26 cells and activated Raw 264.7 macrophage cells. Finally, their study illustrated a convenient, orally administered 6-shogaol drug delivery system that effectively targets colitis tissue, reduces colitis symptoms, and expedites colitis wound repair.

Human studies

Chronic inflammation and Oxidative stress play a key role in ulcerative colitis (UC) onset and severity. A randomized clinical trial in Iran by Bodaghi et al. (2019) examined the short-term effects of ginger on UC and patient's quality of life.

Forty-six patients with active mild to modest UC randomly consumed 500 mg/day of dried ginger powder in four capsules or identical placebo capsules for 6 weeks. They examined the quality

of life, and serum levels of Total anti-oxidant capacity (TAC), High-sensitivity C-reactive protein (hs-CRP), TNF-α, Malondialdehyde (MDA), and nuclear factor kappa B (NF-κB) and the results showed ginger decreased TNF-α and serum MDA factor levels. There were no important changes in inflammatory factors or quality of life. It was concluded that consumption of 2 g of dried ginger root powder for 6 weeks reduces oxidative stress in patients with mild to moderate UC. A 2021 meta-analysis of ginger supplementation on biomarkers of oxidative stress such as glutathione peroxidase (GPx), malondialdehyde (MDA), and total antioxidant capacity (TAC) (Sheikhhossein et al., 2021) showed that ginger supplementation reduced MDA and increased GPx but the outcomes demonstrated that no significant changes in TAC activities. Also, according to the study by Atashak et al. (2011a), Atashak et al. (2011b) ginger un take compared to placebo did not result in a significant change in serum glucose, lipid, MDA and TAC levels.

Another double-blind and randomized clinical trial by Hashemi et al. (Abbas 2020) observed the relationship between ginger and UC. Forty-five patients with mild to modest ulcerative colitis who were separated into two groups received 2,000 mg/day of ginger powder in four capsules or a similar placebo for 12 weeks, and oxidative stress and inflammatory indices were evaluated. The result indicated that the Serum TNF-α levels, Serum MDA, level of hs-CRP, and quality of life were increased considerably after ginger use in cases with UC. This randomized placebo-controlled trial indicated that ginger supplementation of 2000 mg daily could enhance the inflammatory signs of the disease.

Jun et al. (2015) investigated the therapeutic effect of acupuncture combined with umbilical ring point ginger-partition moxibustion for ulcerative colitis of the spleen-kidney yang deficiency type and its impact on related inflammatory factors in ulcerative colitis of the spleen-kidney yang deficiency type. After therapy, serum TNF- and IL-8 levels were shown to be lower in both the control groups and the treatment group, and the reduction in the treatment group surpassed the control group. Acupuncture coupled with ginger-partition moxibustion at the umbilical ring point was shown to be efficacious and safe in the treatment of UC (Table 3), but the number, quality and the overall sample size is too small for definitive conclusions; on the other hand, there is evidence that moxibustion is an inconclusive treatment for UC (Lee et al., 2010). The benefits of ginger in IBD are summarized in Figure 1.

Conclusion and future perspective

In inflammatory conditions of IBD, the migration of inflammatory cells into the colon, such as neutrophils, results in the production of oxidative stress, ROS, and lipid peroxidation. These events affect cell macromolecules and create imbalances in membrane integrity, which can resulting in chronic inflammation, and ulcers (Ajayi et al., 2015). Due to its spasmolytic properties, which are mediated by calcium channel blockade, ginger also has protective effects against UC (Ghayur and Gilani 2005). By inhibiting the peroxidation of lipids, p38 expression, and ginger active compounds also reduce MDA, hydrogen peroxide, and protein carbonyl in a dose-dependent manner (Zhang et al., 2016; Ajayi et al., 2018). A ginger supplement greatly decreased MDA but did not affect TAC. As a result, it may drastically lower the combined SCCAIQ and IBDQ scores (Nikkhah-Bodaghi et al., 2019).

Human studies have some experimental restrictions, such as the high expense of colonoscopies and tissue biopsies. Patients also reported a few minor side effects from taking ginger supplements, such as heartburn and a strong odor. It appears that the supplementation's dosage and duration were too low to result in a noticeable improvement in UC patients, but it improved some aspects of oxidative stress and disease activity. Altogether, more clinical trials using various ginger supplementation doses and durations are required (Nikkhah-Bodaghi et al., 2019).

In summary, ginger and its components efficiently treated IBD by targeting the inflamed intestinal mucosa, blocking damaging factors such as IFN-γ, IL-17, and TNFα despite promoting healing factors like IL-22, IL-10, and TGF-β. Also, ginger had no known side effects and no known herb or drug interactions. These natural products can easily be developed for comprehensive production and may act as an effective therapeutic strategy for preventing and treating IBD. However, further experiments are required to evaluate the safety and efficacy of ginger in IBD treatment, to evaluate the effect of different dosages and durations, to check its regulatory effects on the gut microbiota and, to realize if genetic diversity and environmental agents can influence these activities. Most importantly, RCTs must be designed to study the effect of ginger on Crohn's disease. The result of these studies may open up a novel path in gastrointestinal disorders treatment.

Author contributions

Study concept and design: NiD. Acquisition of data: TM, SO-T, SN, NiD, ZT, and MP. Drafting of the Manuscript: FS, FM, AO, NoD, MV, FN, and SD. Critical revision of the manuscript for important intellectual content: SN. Study supervision: NiD.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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