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REVIEW

Therapeutic Potential of Essential Oils Against Ulcerative Colitis: A Review

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Abstract: Ulcerative colitis (UC) is a chronic non-sp ecific inflammatory disease of the colorectal mucosa. Researchers have associated UC onset with familial genetics, lifestyle behavior, inflammatory immune factors, intestinal microbiota, and the integrity of the intestinal mucosal barrier. The primary therapeutic interventions for UC consist of pharmacological management to control inflammation and promote mucosal healing and surgical interventions. The available drugs effectively control and decelerate the progression of UC in most patients; nonetheless, their long-term administration can exert adverse effects and influence the therapeutic effect. Plant essential oils (EOs) refer to a group of hydrophobic aromatic volatile substances. EOs have garnered considerable attention in both domestic and international research because of their anti-inflammatory, antibacterial, and antioxidant properties. They include peppermint, peppercorns, rosemary, and lavender, among others. Researchers have investigated the role of EOs in medicine and have elucidated their potential to mitigate the detrimental effects of UC through their anti-inflammatory, antioxidant, antidepressant, and anti-insomnia properties as well as their ability to regulate the intestinal flora. Furthermore, EOs exert minimal toxic adverse effects, further enhancing their appeal for therapeutic applications. However, these speculations are based on theoretical experiments, thereby warranting more clinical studies to confirm their effectiveness and safety. In this article, we aim to provide an overview of the advancements in utilizing natural medicine EOs for UC prevention and treatment. We will explore the potential pathogenesis of UC and examine the role of EOs therapy in basic research, quality stability, and management specification of inadequate EOs for UC treatment. We intend to offer novel insights into the use of EOs in UC prevention and management.

Keywords: ulcerative colitis, essential oils, active ingredients, signaling pathway

Introduction

In the clinical setting, patients with ulcerative colitis (UC) present with symptoms, such as abdominal pain, diarrhea, and blood in stool. Often, these symptoms are accompanied by heightened oxidative stress and aggregated cellular inflammatory factors. Furthermore, the course of UC is typically prolonged and prone to recurrence; the long-term chronic inflammatory state increases the risk of developing colon cancer and associated diseases.[1] Data from surveys have indicated a strong correlation between UC prevalence and the level of economic development. Moreover, its incidence is rapidly increasing with the progress of social and economic development. For example, the prevalence of UC ranges from 5.50 to 24.30 per 10,000 globally. UC prevalence in developed countries, such as North America and Europe is approximately 24.30 per 10,000 and 19.20 per 10,000, respectively. By contrast, the prevalence in Asia and the Middle East is approximately 6.30 per 10,000. UC prevalence in mainland China is approximately 11.60 per 10,000, which may be underestimated.[2] Inflammatory bowel disease is more common in industrialized and Western countries; UC has a higher prevalence than Crohn's disease globally and in less developed countries.[3]

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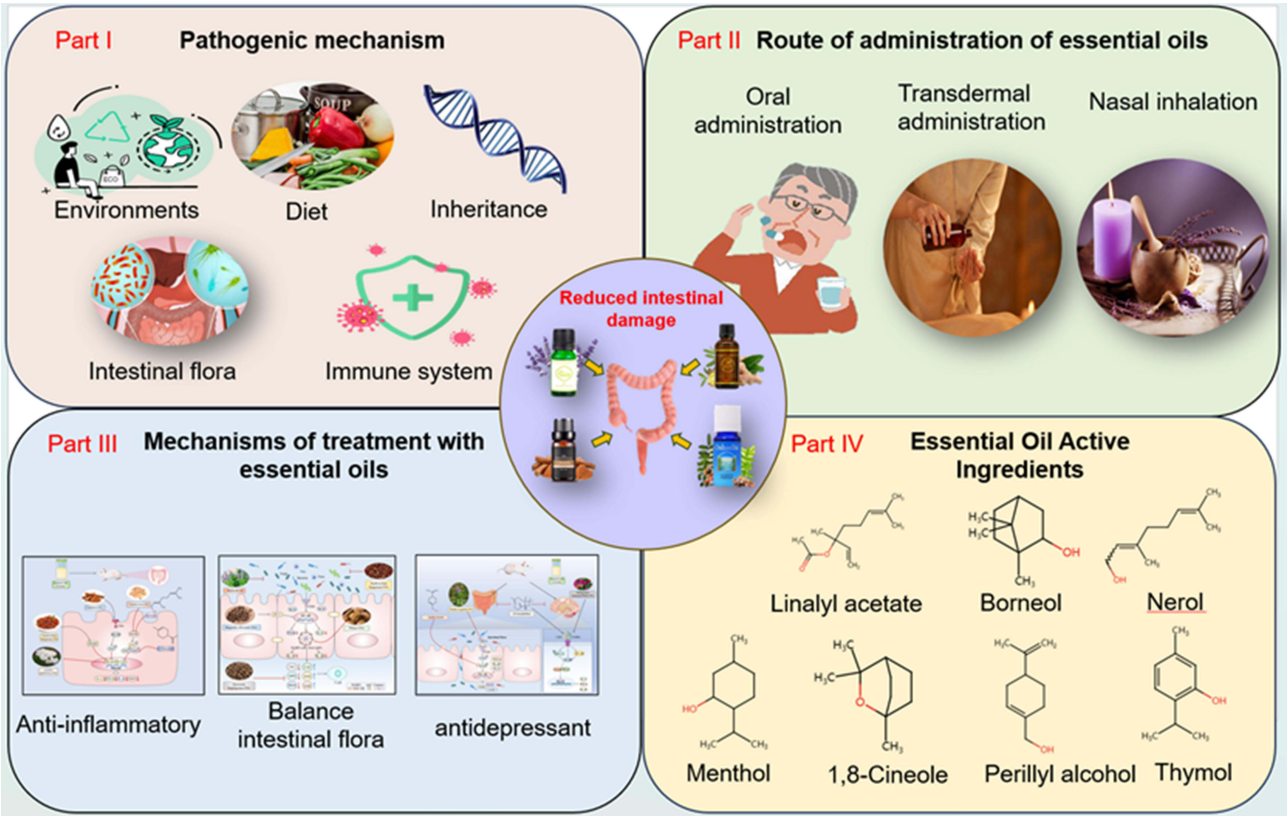
Graphical Abstract



Clinical treatment of UC is based on reducing inflammatory lesions, controlling symptoms, reducing recurrence, and controlling acute exacerbations. The drugs commonly used for UC treatment include aminosalicylic acid (salicylazosulfapyridine, mesalazine), immunosuppressants (azathioprine (AZA)), steroids (methylprednisolone), and biologics (adalimumab, infliximab, bifidobacteria, and bacillus coagulans).[4] However, these drugs are often expensive and display poor therapeutic efficacy. The long-term use of salicylates leads to adverse effects, such as nausea and vomiting. Excess glucocorticoid administration leads to Cushing's syndrome. Moreover, immunosuppressant use can cause bone marrow suppression and opportunistic infections.[5] Considering the adverse effects of traditional medicine use, researchers are investigating effective and inexpensive medicines. Flavonoids, terpenoids, and sulfur-containing compounds in medicinal plants have been identified as potential drugs for the treatment of experimental UC.[6]

Essential oils (EOs), also referred to as volatile oils or ethereal oils, are derived from plant parts, such as flowers, bracts, leaves, branches, roots, bark, fruits, seeds, and resins of herbaceous plants. EOs are extracted through processes, namely distillation, pressing, and solvent extraction. Primarily, they consist of terpenes and aromatic compounds, along with oxygen-containing derivatives, such as alcohols, aldehydes, ketones, phenols, ethers, and endolipids. Additionally, EOs may consist of nitrogen-containing and sulfur-containing compounds. The earliest use of EOs dates back >6000 years to ancient Egypt; archaeologists theorized that Cleopatra used sandalwood, rose, and neroli oils for bathing and anointing. The natives applied EOs all over their bodies after bathing to protect their skin as well as for antiseptic and antibacterial purposes. This is the earliest record of aromatherapy ("Aroma" stands for fragrance in Greek).[7] The extraction, composition analysis, and functional properties of EOs have gained attention because of their antimicrobial, antiviral, antioxidant, and neuromodulatory effects.[8–10] Researchers have demonstrated new advancements in UC treatment using EOs. Ghasemi-Pirbaluti et al[11] demonstrated that the administration of menthol, the active ingredient of peppermint EO, improved the gross signs of UC in rats. It improved hematocrit levels and histopathology and

significantly reduced the levels of interleukin (IL)-1β, IL-6, tumor necrosis factor alpha (TNF-α), and myeloperoxidase (MPO) in the colon. Additionally, menthol was effective in preventing acetic acid-induced UC in rats. In a therapeutic model of oxazolone-induced colitis, Agastache Mexicana EOs[12] significantly reduced abdominal writhing in rats; limonene and thujone were the primary bioactive metabolites in this model. EOs of *Atractylodis caryophyllus* and Hainan sandalwood have demonstrated ameliorative effects in UC.[13,14] EOs can stimulate the olfactory nerves, which in turn affects the central nervous system and endocrine system. Consequently, it regulates immune function and exhibits antioxidant and anti-inflammatory capacities in UC. However, this view is primarily based on theoretical experiments, thus necessitating additional clinical studies to determine the efficacy and safety of EOs in UC treatment. A limited number of reviews have reported on the utilization of EOs in UC management. This article presents a comprehensive synthesis of contemporary research on EOs for UC treatment, encompassing the application of plant EOs, their monomer components, and the comparative benefits of conventional therapies. We aim to establish a theoretical framework to utilize EOs in UC treatment and to furnish an enhanced theoretical foundation for future treatment endeavors.

Potential Pathogenesis of Ulcerative Colitis

Environmental Factors

In recent years, the incidence of UC has been increasing, especially in developing countries. Nutritional imbalance and dietary factors play an indispensable role in the changes of intestinal flora, the damage of mucosal barrier and the regulation of immune response. Many factors such as environmental hygiene and living habits also increase the risk of UC. In the psychological aspect, if people's mental state is in a high-pressure, stressful situation for a long period of time, then the adrenal axis, mucosa, and pathogens will interact with each other, which will contribute to the activation of the activity of intestinal mucosal mast cells and the production of more hormones that cause intestinal inflammation, which will ultimately lead to the triggering of UC.[15] Appendectomy can increase extraintestinal symptoms of UC.[16] Histological analysis shows that aging can cause steatosis of appendiceal lymphoid tissue, and appendiceal lymphoid tissue in patients with UC is more prone to steatosis, and the inactivation of appendiceal lymphoid tissue degeneration can further exacerbate the onset and development of UC.[17] Through the in-depth understanding of the intestinal flora and intestinal mucosal immune system, the appendix can provide a rich nutrient for the normal intestinal flora for the organism and protect the intestinal lumen from pathogenic bacteria.[18]

Dysbiosis of Intestinal Flora

More and more studies have found that intestinal flora dysbiosis plays an important role in the pathogenesis of UC, so this factor is also a focus of research in the study of the pathogenesis of UC. Gut flora is the most abundant microbiota in the human body, and most human gut microbiome consists of four phyla, ie, Sclerotinia, Anaplasma, Aspergillus, and Actinobacteria.[19] Also, gut microbes produce metabolites with anti-inflammatory effects, such as short-chain fatty acids (SCFA), and through the metabolites, they provide nutrients and energy to the body and modulate the immune system thereby protecting the host.[20,21] The gut microbiota is involved in the development and progression of UC by mediating a variety of relevant immune-inflammatory pathways. Disruption of the balance of beneficial and harmful flora in the gut microbiota, ie, dysbiosis, is associated with the development of colitis.[22] When suffering from ulcerative colitis, the proportion of short-chain fatty acid-producing thick-walled bacterial phylum and Clostridium spp. in the intestine decreases, while probiotics are significantly reduced while pathogenic bacteria increase, and their release of enterotoxins can disrupt the integrity of the intestinal epithelium, leading to increased permeability of epithelial cells.[23] At the same time, the reduced diversity of the intestinal flora, the decrease in SCFA, and the increase in the intestinal flora releasing inflammatory mediators activate the immune activity of the intestinal mucosa, resulting in a persistent localized inflammatory response.[24] Although the pathogenesis of UC is not fully understood, intestinal microecological imbalance influences the development of UC at multiple levels.

Immune Factors

Abnormal immune function is an important factor in the pathogenesis of UC. Imbalance of intestinal flora, overreaction of mucosal immune system and inability of mucosal defense mechanism to inhibit inflammatory stimuli will involve innate or adaptive immune response, which is mainly manifested in epithelial cell damage, intestinal barrier dysfunction, autoimmunity, abnormal expression of cytokines, and immune cell infiltration. When the local microenvironment of the intestinal tract changes or is stimulated by exogenous stimuli, it will activate the innate and adaptive immune mechanisms, promote the synthesis and secretion of immune molecules, and induce the activation of immune cells to initiate the immune defense response. UC is induced when the body is repeatedly attacked by pathogens resulting in the activation and expansion of specific T cells, disrupting the balance between T cell subsets and driving excessive inflammatory responses.[25] With increasing research, the role of inflammatory vesicles in the immune system is gradually being recognized. Different inflammasomes are expressed in both immune and non-immune cells. Inflammatory vesicles act as protein sensors in response to pathogens and are the first participants in the innate immune system, recruiting innate inflammatory factors and subsequently activating adaptive immune responses.[25–27]

UC Pathogenesis and the Limitations of Marketed Drugs

The primary clinical manifestations of UC include abdominal pain, diarrhea, mucus, pus, and blood in stool, which may be accompanied by systemic reactions, such as fever, malnutrition, and other extraintestinal manifestations. The lesions primarily affect the mucosa and submucosa, usually beginning in the rectal mucosa, developing retrograde to the proximal segment, and spreading to the entire colon in severe cases. Moreover, recurrent and prolonged intestinal inflammation and ulcers in UC increase the risk of colorectal carcinogenesis, which not only reduces the quality of patient survival but also imposes a serious healthcare burden.[28] The acute exacerbation of severe colitis occurs in approximately 15% of the patients with UC, of which 30% require colectomy.[29] UC is typically treated using Western medicine with chemical drugs, such as glucocorticoid hormones, aminosalicylic acid preparations, and immunosuppressive agents. These drugs are preferred for mildly and moderately active patients. Furthermore, they are used as maintenance drugs for patients in remission; nonetheless, they exert substantial adverse effects, tend to make the patients dependent and generate poor clinical outcomes. 5-aminosalicylic acid (5-ASA) is a well-tolerated drug; the oral administration of 2 g to 3 g of 5-ASA daily is sufficient for most patients with mildly to moderately active UC. Additionally, clinicians use immunosuppressive drugs in UC treatment because they suppress the immune system. AZA, methyl methacrylate, and 6-mercaptopurine are commonly used for UC treatment. These drugs are clinically indicated only in patients who underwent failed glucocorticoid or aminosalicylic acid therapy or in patients who cannot tolerate the adverse effects of drugs. Thiopurines were identified in a Spanish database study. Thiopurine administration may cause nausea (8%), hepatotoxicity (4%), bone marrow toxicity (4%), pancreatitis (4%), non-melanoma skin cancer, and lymphoma.[30] Biologics effectively treat UC and are well tolerated by individuals, with few adverse effects. Moreover, they provide an alternative approach to UC treatment. Infliximab is preferred for clinical use. Duan Zexing et al[31] used infliximab to treat patients with moderate-to-severe UC; the clinical symptoms were significantly relieved after 8 weeks and the mucosal healing rate was high. Moreover, no serious adverse effects were observed during the study; nonetheless, the price of the drug was high. The clinical methods to improve intestinal flora in healthy individuals primarily consist of antimicrobial drugs, probiotics, prebiotics, and fecal transplantation. Probiotics are the most commonly used microecological agents in clinical practice. They refer to a group of biologically active microorganisms that are beneficial to the body when ingested appropriately. Probiotics can inhibit pathogenic bacteria, strengthen the intestinal mucosal barrier, and regulate immune response.

Researchers have reported on limited drugs with considerable efficacy, few adverse effects, and suitable prices. Among natural medicines, EOs with wide distribution, high content, low toxicity, and good anti-inflammatory effects can be used as an alternative for UC treatment in the future.

Routes of Essential Oils Administration

EOs therapy is implemented in numerous ways, including fumigation, bathing, massage, gua sha, inhalation, oral administration, and other methods, through the sense of olfaction, gustation, and tactile functions. EOs are absorbed through the skin, digestive, and respiratory systems; they regulate the central nervous system, circulatory, and endocrine

systems to restore the coordination of the body and mind to eliminate depression, anxiety, boredom, anger, and fatigue-related emotions and feelings. Vegetable EOs have antibacterial and antiseptic functions; thus, they are widely used in food and medicine.[32]

Oral Route of Absorption

The advantages of drug absorption through the oral mucosa include convenient administration, rapid absorption, and entry to the internal jugular vein through numerous capillaries under the oral mucosa. Moreover, they reach the heart directly without passing through the liver. Wang et al[33] reported that lavender EOs administered via gavage alleviated colonic mucosal injury in dextran sulfate sodium (DSS)-induced colitis experiments in mice. Furthermore, it reduced the inflammation of epidermal growth factor receptor, TNF-α, and IFN-γ levels of cytokines. Zhou et al[34] used ginger volatile oil to gavage mice with peritonitis; ILs secreted by peritoneal macrophages were significantly reduced in the experimental group, resulting in controlled inflammatory response. Cinnamon EOs can treat renal diseases and rheumatic diseases. Wang et al[35] administered cinnamon EOs to rats with hyperuricemia via gavage; the rats presented with reduced uric acid weakened hepatic xanthine oxidase activity, and increased superoxide dismutase and glutathione peroxidase levels, which improved renal injury. EOs can improve insomnia symptoms. Li et al[36] reported that the oral administration of rosemary hydrosol significantly increased the serum levels of 5-hydroxytryptamine (5-HT), gamma-aminobutyric acid (GABA), and dopamine in rats with insomnia. Furthermore, it increased the levels of serotonin 1A receptor, cyclic adenosine monophosphate (cAMP)-dependent protein kinase, GABA, cAMP, and adenylyl cyclase 5 proteins in the hippocampus (HP), which elevated the duration of sleep.

Nasal Route of Administration

The nasal administration of EOs is a convenient route of drug administration. Its inherent advantages consist of a large surface area for absorption, rich vascularity of the nasal mucosa, and rapid entry of drugs into the circulatory system through the nasal cavity, which can bypass the hepatic first-pass effect. Wu et al[37] demonstrated that EOs inhalation altered the brain metabolism in rats, with increased carbohydrate levels and decreased neurotransmitters, amino acids, alcohols, and fatty acid levels. By contrast, the nucleoside and lactic acid content increased in urine; these changes were considered beneficial to the anti-anxiety response in rats. According to Li et al[38], reported the inhalation of lavender EOs could inhibit 5-HT-related receptors and block the Ca2+/ calcium/calmodulin-dependent protein kinase II/extracellular-signal regulated kinase1/2 pathway downstream of the cAMP signaling pathway in a rat model of xenophobia, thus exerting an antiemetic effect. Cui et al[39] reported that aluminum trichloride induced anxiety in rats that inhaled and sniffed bergamot EOs, which increased the frequency of entry into the central region, walking distance, open-arm time, and frequency, γ-aminobutyric acid levels, and antioxidant activity in the HP and frontal cortex (FC). Furthermore, it decreased the levels of propylene glycol, a lipid peroxidation product, and inflammatory factors in the HP and FC. Thus, bergamot EOs may alleviate anxiety through antioxidant, anti-inflammatory, and GABA-modulatory effects. The nasal inhalation of EOs serves as a complementary alternative therapy in the neurological, digestive, respiratory, and cardiovascular systems. However, some aromatic EOs can cause neurotoxicity, hepatotoxicity, gastrointestinal irritation, phototoxicity, contact sensitization, and other adverse effects.

Transdermal Route of Administration

Transdermal administration is a common mode of essential oil delivery, which has the advantages of high bioavailability, low adverse effects and good patient compliance.[40,41] Li et al[42] human in the treatment of DNCB-induced atopic dermatitis with rosemary EOs, observed improved skin lesions in mice coated with rosemary essential oil, a significant reduction in serum IL-6, TNF-α, as well as in skin tissues with decreased expression of p-JAK1, CD4+ cells, IL-4, p-P65/P65, p-STAT3/STAT3 protein expression was reduced. Pires F Q et al[43] utilized HP-β-CD and nanostructured lipid carrier (NLC) for encapsulation of EOs, which solved the problem of volatility and solubility of EOs while achieving the control of the drug release rate and improved the utilization of EOs for transdermal administration. Rafii et al[44] found that massage with lavender and chamomile EOs had a favorable effect on anxiety and improved the quality of sleeping in burn patients. Nasiri et al[45] had patients with osteoarthritis of the knee joints undergo

self-massage with lavender oils for nine times over a three-week period and found that the severity of pain in patients of the intervention group There was a significant difference in the severity of pain immediately after the intervention and 1 week after the intervention, but not at the fourth week follow-up, probably because the effects of the EOs wore off over time. Transdermal drug delivery is simple to learn and easy to administer, is increasingly accepted by patients, and is widely used in clinical nursing practice. Because of its use of EOs as a medium for massage, in addition to the therapeutic effect of EOs themselves, it can also increase the comfort brought to patients by simple massage, which is conducive to the establishment of a good nurse-patient relationship, and it can be said that it is an important research direction for the future of non-pharmacological therapies.

Use of Essential Oils in UC Treatment and Its Complications

Anti-Inflammatory Effects

Inflammation refers to a local protective response of the infected cells and adjacent tissues to irritation, injury, or infection; it is characterized by pain, redness, swelling, and the loss of cell function in severe cases.[46] Plant EOs have anti-inflammatory activity[47] and are central to UC treatment (Figure 1). Shiso aldehyde, the active ingredient in *Perilla frutescens* EOs, exerts an inhibitory effect on inflammation. Uemura et al[48] investigated the anti-inflammatory activity of perilla aldehyde in a mouse model of DSS-induced colitis; its administration inhibited the expression of DSS-induced colonic factor genes and matrix metalloproteinase 9 and improved intestinal inflammation. Nuclear factor kappa B (NF-κB) controls the gene regulation of numerous inflammatory factors. Moreover, NF-κB effectively controls UC inflammation.[49] *Ocimum basilicum* EOs inhibit acetic acid-induced colitis in rats by reducing leukocyte aggregation

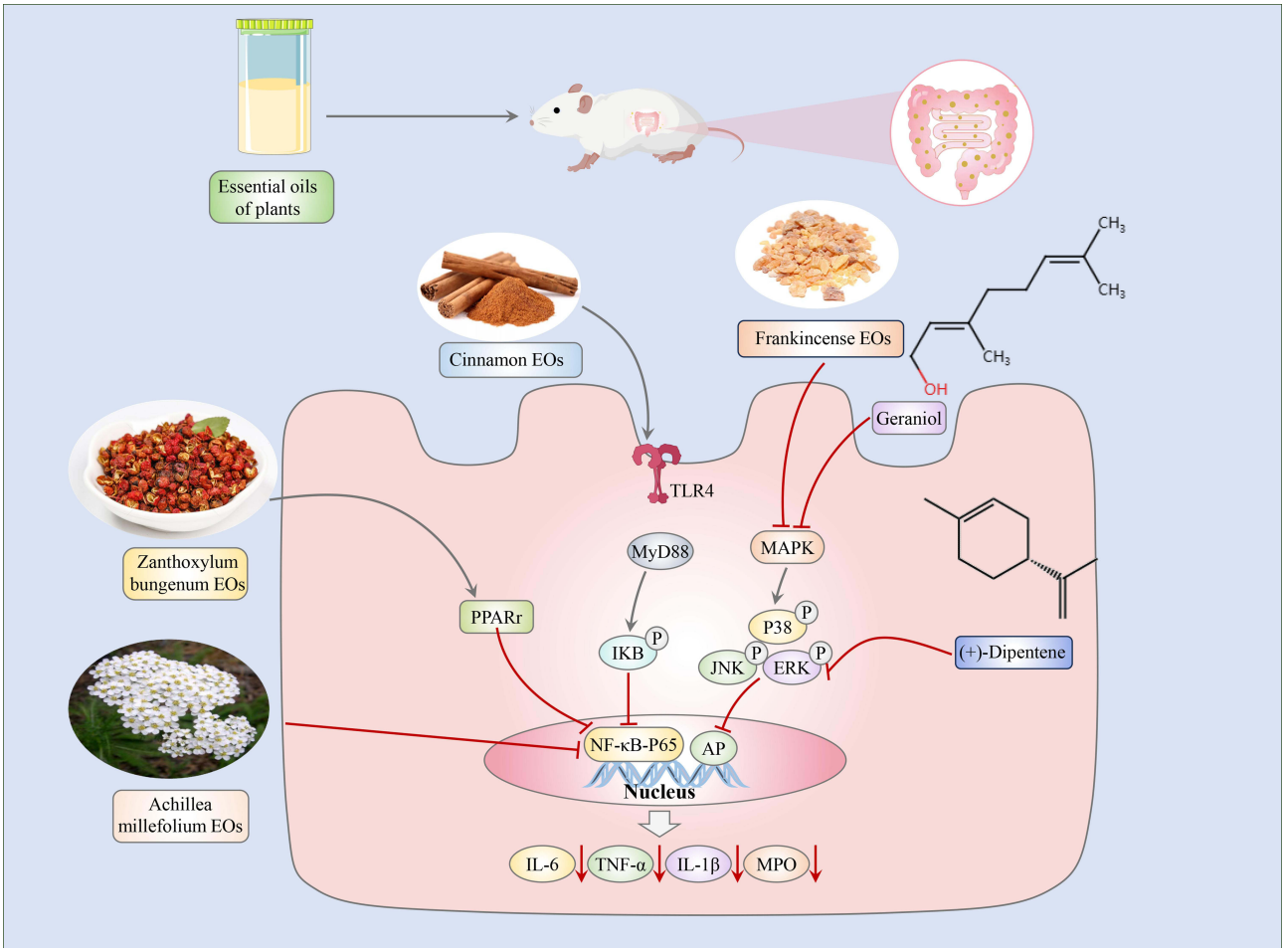


Figure 1 Essential oils modulate different signaling pathways to exert anti-inflammatory effects.

and inhibiting myeloperoxidase production.[50] *Foeniculum vulgare* EOs[51] attenuates acetic acid-induced colitis in rats by inhibiting NF-κB. This anti-inflammatory effect may be attributed to its active ingredients, such as trans-anethole brain and D-limonene, which inhibit NF-κB activation(Table 1). Compound EOs can exert synergistic efficacy to alleviate UC. Shishenwan volatile oil, which is composed of tonicolium, nutmeg, Wuzhu, and Schisandra volatile oils, effectively improved UC symptoms in mice, with a significant increase in body mass and decreases in disease activity index (DAI) scores, inflammatory cell infiltration, and colonic mucosal injury.[52]

Effects on the Intestinal Flora

The intestinal microenvironment is primarily composed of intestinal microbiota and mucosal cells, which can participate in physiological and pathological activities through four aspects as follows: intestinal microbial, chemical, mechanical, and immune barriers.[53] These barriers are central to maintaining intestinal health. Impaired intestinal barriers increase the permeability of the intestinal mucosa to harmful bacteria, causing an imbalance in the intestinal flora, and leading to intestinal inflammation.[54] Intestinal inflammation is related to UC pathogenesis.[55] Adherent and invasive Aspergillus fungi are involved in altered intestinal dysbiosis, exploiting host defenses and inducing pro-inflammatory changes. Eventually, they lead to dysbiosis of the intestinal flora.[56] Additionally, *Streptococcaceae* and *Enterobacteriaceae* are abundant in UC models; their abundance has been associated with increased inflammatory responses. EOs may reduce UC severity by modulating the microenvironment of the parietal gut and restoring intestinal integrity (Figure 2). The oral administration of stigmasterol reduced the levels of Aspergillus phylum, Enterobacteriaceae, and *Streptococcus pepticus*,

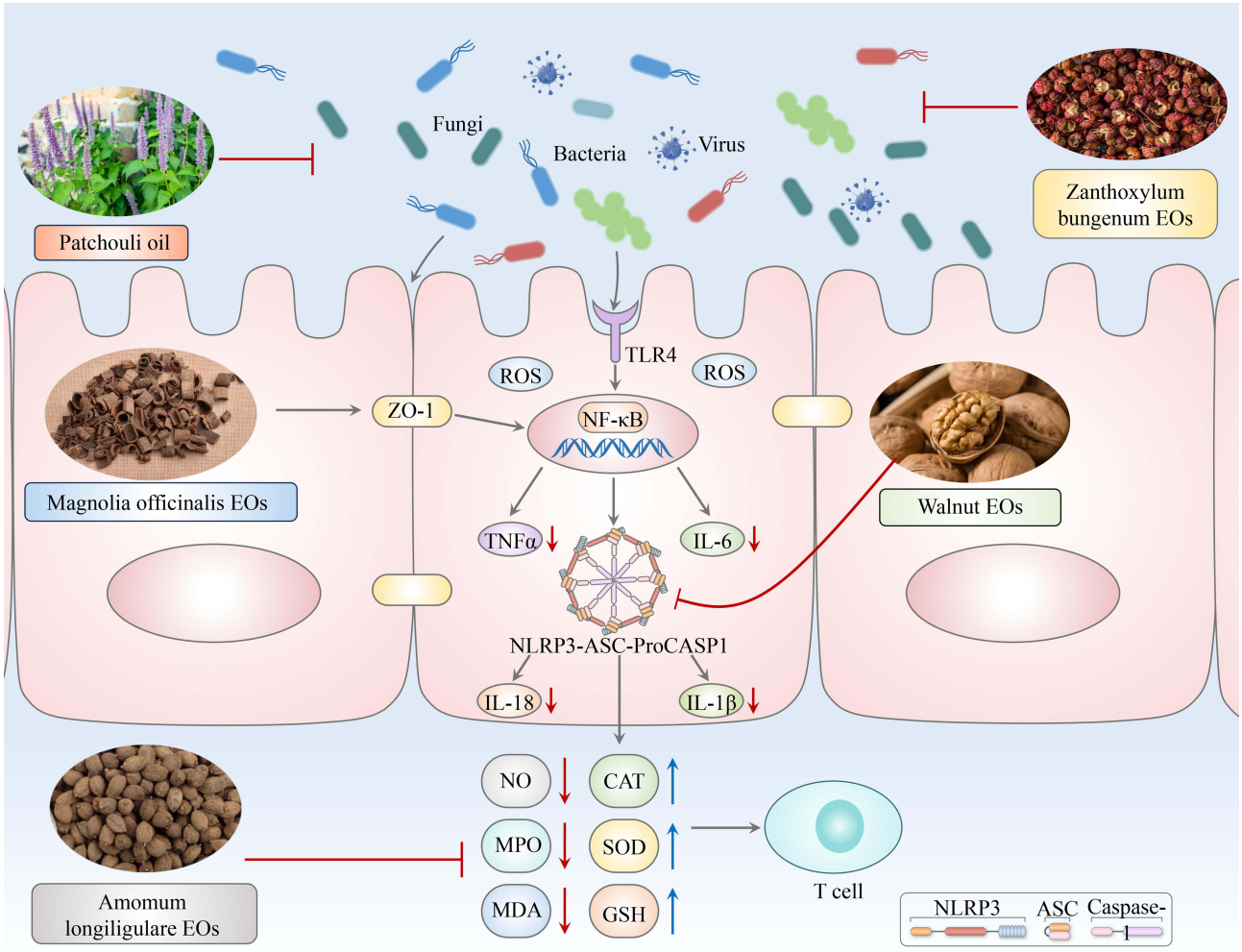


Figure 2 Essential oils balance the gut microbiological environment.

thereby modulating the intestinal flora to alleviate DSS-induced UC. Several studies have demonstrated decreased levels of Lactobacillus and Bifidobacterium and increased levels of *Escherichia coli (E. coli)* in patients with colitis and DSS-induced colitis in mice.[57,58] The use of peppercorn EOs[59] modulated changes in bacterial composition and significantly reduced DSS-induced elevated *E. coli* levels. Treatment with aromatic turmeric ketone reduced Helicobacter pylori and Desulfovibrio family levels. Aromatic turmeric ketone is effective in UC treatment; it prevents DSS-induced damage of the intestinal flora, maintains some beneficial bacteria, and reduces harmful bacteria.[60] A diet rich in n-6 unsaturated fatty acids (PUFA) increases the microbiota in mice, which induces inflammation and exacerbates infections causing colitis. However, the addition of n-3 PUFA to a diet rich in n-6 PUFA converts the pro-inflammatory microbiota to anti-inflammatory microbiota, thereby preventing colitis. Some of the chief components of EOs can be added to the daily diet to maintain gut microbial balance and provide novel ideas for treatment (Table 1).

Antioxidant Effects

Reactive oxygen species (ROS) primarily refers to highly reactive oxygen-containing substances, such as superoxide anion (O_2^-), hydroxyl radical (OH^-), and hydrogen peroxide (H_2O_2). Reactive oxygen radicals oxidize the biomolecules of intestinal epithelial cells, destroy the mechanical barrier of the intestinal mucosa, and cause pathophysiological processes, such as bacterial translocation, intrinsic immune damage, mitochondrial dysfunction, and iron death. Moreover, they promote the development of UC.[61,62] Many EOs have both anti-inflammatory and antioxidant effects and can be used to treat UC (Figure 2). Bergamot lactone, the active ingredient of bergamot EOs, can reduce TNF-α, IL-1, and IL-6 levels in rats. Additionally, it can significantly reduce oxidative damage by attenuating the increase in malondialdehyde (MDA) and 8-hydroxydeoxyguanosine levels as well as by restoring the decrease in antioxidant enzyme levels.[39] The EOs of *Salvia miltiorrhiza*[63] significantly increased superoxide dismutases and glutathione peroxidase activities and decreased nitric oxide synthase levels in the colon tissues of UC rats, suggesting the antioxidant capacity of VOA to accelerate the scavenging of free radicals and attenuate the damage caused by oxygen free radicals and lipid peroxidation in colon tissues (Table 1). Perillyl alcohol displays anti-inflammatory and anti-tumor activities. Additionally, it exerts antioxidant effects, prevents NF-κB activation, and reduces the production of pro-inflammatory cytokines because of its ROS-scavenging properties.[64]

Antidepressant Effects

The development of the "biopsychosocial" medical model has directed attention toward the role of psychosocial factors in UC pathogenesis and treatment. UC has been recognized as a physical and mental disease. Patients with UC often present with numerous abnormal psychological states, predominantly characterized by anxiety and depression. Its pathogenesis may be related to the brain-intestinal axis. Moreover, these psychiatric factors affect the neuropituitary, endocrine, intestinal immunity, and other functions, causing changes in intestinal inflammation and UC occurrence and development.[65] Aromatic olfaction therapy is widely used because of its ease of operation and beneficial effects on relieving bad moods. It is expected to become a useful supplement to traditional medical treatments. The aroma components of plant EOs positively affect mood regulation.[66] Compared with chemical antidepressants, EOs of natural medicines can achieve the goal of multi-targeted depression treatment using pharmacological components (Figure 3). They can mimic the effect of antidepressants while reducing adverse effects, which is valuable for the development of new antidepressants and the prevention of UC.[67] Citronellol and geraniol, the chief components of geranium EOs demonstrate some antidepressant effects.[68] The etiology of UC is unclear; nonetheless, researchers have reported a bidirectional relationship between psychological co-morbidities and UC treatment, which coexist to influence the disease course. The use of plant EOs for aromatherapy can alleviate anxiety and depression. Moreover, clinicians should not ignore patients with UC along with depression and other psychological problems, particularly active intervention and treatment (Table 1).

Anti-Insomnia Effects

Insomnia refers to the subjective experience of patients who are dissatisfied with the duration or quality of sleep; it affects daytime social functioning. Insomnia is a common sleep disorder. Impaired daytime functioning is the chief

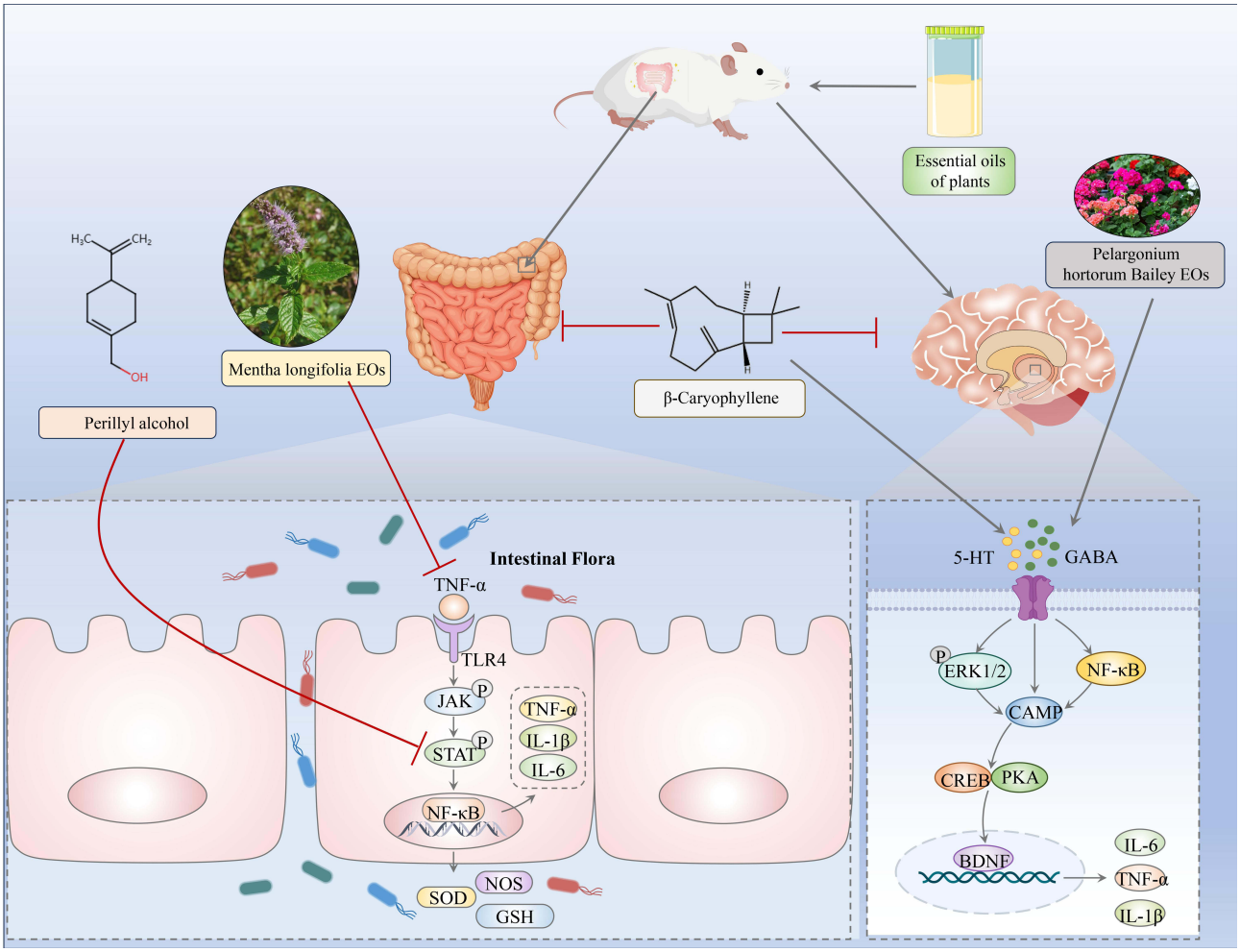


Figure 3 Essential oils inhibit inflammation in ulcerative colitis through antidepressant effects.

reason for clinic visits. The purpose of treatment is to improve the quality of sleep and restore daytime functioning in patients. However, insomnia is not only a sleep problem; particularly, chronic insomnia poses the risk of major diseases (such as anxiety disorders, depression, hypertension, diabetes, dementia, and cancer) and is often co-morbid with somatic and psychiatric disorders.[69] Some studies have demonstrated a bidirectional association between sleep deprivation and UC. Poor sleep quality may increase the severity of UC inflammation and the risk of recurrence.[70] Thus, aromatherapy is used as a safe and effective non-pharmacological therapy to improve sleep quality in patients with insomnia (Figure 3). Chien et al administered lavender through inhalation for 12 weeks in 67 women with sleep disorders. These volunteers were aged from 45 to 55 years. After 12 weeks, they were instructed to inhale lavender EOs using water as a blank control, twice a week, 20 min each time. After 1 week, lavender EOs improved the condition of sleep disorders. Koo et al[71] significantly prolonged the time of sodium pentobarbital-induced sleep in mice after inhaling 10h of essential oil of Acorus calamus. Changes in the content of γ-aminobutyric acid in mice's brains may exert a sedative-hypnotic effect. Aromatic EOs therapy can effectively improve the sleep quality of patients with UC along with insomnia; thus, it is a safe and feasible therapeutic and nursing intervention (Table 1).

Mechanisms Underlying Anti-UC Action of Plant Essential Oils

Regulating the NF-κB Signaling Pathway

The NF-κB signaling pathway is a classical inflammatory signaling pathway that regulates the expression of inflammatory factors and cell surface receptors. Moreover, it participates in immune and inflammatory responses. Under

Table 1 Mechanism of Action of Essential Oils in the Treatment of Ulcerative Colitis

Plant Name	Essential Oil Main Ingredients	Dose/Course of Treatment	Animal Model	Mechanisms	References
Foeniculum vulgare	Trans-anethole (81.08%), turnip ketone (9.66%), methylcholesterol (4.74%), D - limonene (4.09%),	Oral administration for 5 days 100, 200, 400mg/kg	Acetic acid-induced colitis in rats	NF-κB signaling pathway	[51]
Zanthoxylum bungeanum Pericarp	Terpinen-4-ol (25.34%), eucalyptol (21.82%), and xanthoxylin (14.77%)	Oral administration for 14 days, 20.40 and 80 mg/kg	DSS-induced colitis in mice	Protecting the intestinal barrier anticancer NF-κB/PPARγ signaling pathway	[59]
Geranium (Pelargonium graveolens)	β-citronellol (33.4%), geraniol (17.5%), γ-eudesmol (6.8%), linalool (6.5%) and menthone (6%)	Oral administration for 4 days, 100, 200 and 400 mg / kg	Acetic acid-induced colitis in rats	Anticancer antioxidant	[72]
Lavender	β-laurene (9.64%), 3-carene (7.54%), β-lorene (6.2%), linalool (21.99%)	Oral administration for 7 days, 12.5, 25, 50 mg kg-1 day-1	DSS-induced colitis in mice	Th17 cell differentiation signaling pathway	[33]
Achillea millefolium	Daganocarpene D (26.15%), Pinene (14.28%), β-pinene (11.40%), β - stigmasterol (10.35%), Matricaria azulene (10.04%),	Oral administration of 100 mg/kg for 9 days	DSS-induced colitis in mice	NF-κB/PPARγ signaling pathway	[73]
Oregano (*Origanum vulgare L.*)	Carvacrol (64.3%), Linalool (13.8%), p-Cymene (7.1%)	Rectal drip for seven days, 1 mg / kg day^{-1}	TNBS-induced colitis	Anticancer	[74]
Rhizoma Atractylodis	β-aminolevulinol, diphenyl-4-carbaldehyde, β-aminolevulene, α-aminolevulinol and maitake alcohol	Oral administration for 7 days, 1, 2, 4 g/kg	TNBS induces colitis in rats	Down-regulation of MPO activity and inflammatory factor expression in colon tissue Increased number of cup cells	[13]
Tangerine peel	Limonene, α-pinene, γ-pinene, β-laurene accounted for	Intraperitoneal injection 7 days, 0.571, 1.142, 2.283 mg/kg	Acetic acid-induced colitis in rats	TNF-α, CD4+ and CD8+ were decreased in colon tissue	[75]
Hainan sand nut (*A. longiligulare T. L. Wu*)	Bornyl acetate, camphor, naphtha	Oral administration for 21 days, 0.42, 0.84 and 1.68 g-kg-1	Preparation of UC rat model by DNCB plus acetic acid enema method	Inhibition of TNF-α release Reduction of NF-κBp65 expression NF-κB signaling pathway	[63]
Bunium persicum	γ-Terpinene, p-Cumin aldehyde, Cuminic alcohol	Oral administration for 5 days, 100, 200, 400 mg/kg	Acetic acid-induced colitis in rats	Inhibition of NF-κB pathway, reduction of inflammatory factors and MPO activity NF-κB signaling pathway	[76]
Fresh ginger	Gingerene (28.05%), arylgeranylene (14.06%), α-bisabicyclohexene (12.91%), β-erythromycin (13.15%), and chamazulene (9.32%).	Oral administration of 100, 200 and 400 mg/kg for 5 days	Acetic acid-induced colitis in rats	Antioxidant, inhibits nitric oxide, inflammatory cytokines and enzymes	[77]
Cinnamon	Cinnamaldehyde, alpha-pinene, benzaldehyde	Oral administration for 13 days, 10, 15 mg/kg	DSS-induced colitis in mice	Reduced Helicobacter pylori spp. and Mycobacterium avium spp. and promoted intestinal probiotics Downregulation of TLR4 signaling and IL-6 and TNF-α, but upregulation of IL-10	[78]

Agastache rugosa (botany)	β-Patchouliene, α-guaiacene, patchouli alcohol, patchouli ketone	Rectal drip for 7 days, 65,135 and 270 mg/kg	TNBS-induced colitis	Attenuated inflammatory cell infiltration Regulation of intestinal microorganisms	[79]
Ocimum basilicum L. var. pilosum (Willd.) Benth.	Linalool (39.73%), β-pinene (6.65%), trans-verbenol 6.39%), and α-terpinolene (5.03%).	Oral administration, 100, 200, 400 μL/kg for five days.	Acetic acid-induced colitis in rats	Reduces leukocyte aggregation Inhibition of MPO activity	[50]
Mentha longifolia	Eucalyptol (33.4%) and pulegone (40.7%) cis-pulegone oxide (2.5%), epoxy-p-mentha-1,8(10)-diene (2.4%), menthone (2.4%),	Oral administration for 3 days, 100, 500, 1000mg/kg	Acetic acid-induced colitis in rats	Antioxidant Reduces MPO activity Reduced expression of TNF-α	[80]
Thickets	β-Eudesmol, α-Eudesmol, Pinene	Oral administration for 7 days, 6.5, 26 mg/kg	DSS-induced colitis in mice	Inhibition of inflammatory factors such as TNF-α and IL-1β Increased expression of Occludin, Claudin-1 tight junction proteins improves colonic mucosal barrier injury	[81]
Pistacia lentiscus	α-pipene, β-pipene, β-myrcene, linalool, trans-caryophyllene	Oral administration for 6 days, 400 mg/kg/day	Acetic acid-induced colitis in rats	Anticancer Inhibition of MPO activity	[82]
Chimonanthus nitens Oliv	3-(4,8-Dimethylnona-3,7-dienyl)-furan, camphor, long leaf aldehyde	Oral administration for 9 days, 50, 100, 200 mg/kg/day	DSS-induced colitis in mice	Antioxidant	[83]
Musa acuminata pericarp	Isoamyl isobutyrate (18.3%), n-hexadecanoic acid (22.05%), myristicin 9.31%	Oral MA extract treatment for 14 days, 250 and 500 mg / kg	Acetic acid-induced colitis in rats	MA pericarp was most effective in its ability to prevent the development of severe ulcerative colitis.	[84]
Garlic	Propyl propylene disulfide, propylene disulfide, propylene trisulfide	Oral administration for 7 days, 15, 25, 50 mg/kg	DSS-induced colitis in rats	Possesses antioxidant, anti-inflammatory and immunomodulatory properties	[85]
Brucea javanica	Brusatol	Oral administration for 7 days, 152.5 mg/kg, 305 mg/kg, 610 mg/kg	DSS-induced colitis in mice	Prevention of inflammation of the colon Enhancement of intestinal epithelial barrier function NF-κB signaling pathway RhoA/ROCK signaling pathway	[86]
Extra virgin olive	Squalene, Total sterols	Oral 5% extra-virgin olive oil at one-week intervals, repeated three times	DSS-induced colitis in rats	Good anti-inflammatory properties Inhibition of enhanced expression of STAT3, p-STAT3, COX-2 and iNOS	[87]
Walnut	Linoleic acid, alpha-linolenic acid	Oral administration for 9 days, 2.5 mL/kg	DSS-induced colitis in mice	Inhibition of ROS generation Mediates the NLRP3/ASC/Caspase-1 signaling pathway Regulates intestinal flora and SCFAs levels	[88]
Rosmarinus officinalis L	L-alpha-pinene, alpha-pinene, eucalyptol	Oral administration REO-microemulsion for 10 days, low-dose (125 mg/kg、250 mg/kg、500 mg/kg).	DSS-induced colitis in mic	L-alpha- terpineol, alpha-pinene and eucalyptol in REO-ME inhibited the release of inflammatory factors by modulating the key targets within the IL-17 signaling pathway, HSP90AA1, IKBKB, and RELA, treating UC	[89]

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unstimulated conditions, NF-κB is attached to NF-κB inhibitors (IκB), and its component heterodimers are retained in the cytoplasm in an inactive form.[90] However, upon stimulation by inflammatory factors, NF-κB is released into the nucleus via the phosphorylated degradation of IκB and P65 and encodes various cytokines and chemokines, which initiate target gene expression, such as TNF-α, IL-1β, and others contributing to the activity of NF-κB signaling pathway.[91] Amir et al[92] demonstrated that *Bunium persicum* EOs (200 mg/kg and 400 mg/kg) reduced MPO and TNF-α activities in rat colon tissues. Additionally, they inhibited acetic acid-induced p-NF-κB protein expression; this anti-inflammatory activity may be attributed to cuminaldehyde, γ-terpinene, and p-cymene. According to Maged et al[73] treatment with yarrow EOs in UC mice significantly increased the anti-inflammatory cytokine IL-10 and decreased the inflammatory cytokine IL-6 levels and NF-κB expression and TNF-α. Zhang et al[59] reported that pepper EOs activated peroxisome proliferator-activated receptor gamma (PPAR-γ), and, thus, inhibited the expression of NF-κB, TNF-α, IL-1β, and IL-12 and reduced DSS-induced colon injury. Zheng et al[93] demonstrated that *Brucea javanica* oil, which is rich in brusatol, reversed DSS-induced p65 phosphorylation in a dose-dependent manner, thereby inhibiting NF-κB activation.

Regulating the (TLR)4 Signaling Pathway

Toll-like receptor (TLR)4 is an important signaling pathway that mediates inflammatory responses in the body. Upon stimulation, TLR4 recognition of pathogen-associated molecular patterns is activated, allowing the recruitment of myeloid differentiation protein and triggering a signaling cascade that induces NF-κB activation.[94] Furthermore, it regulates the expression of pro-inflammatory factors, such as IL-6 and IL-1β, which promote inflammatory responses.[95] Li et al[78] demonstrated that the oral administration of cinnamon EOs in mice with colitis downregulated TLR4 signaling, IL-6, and TNF-α, increased the anti-inflammatory cytokine IL-10, and displayed potential antimicrobial activity in inhibiting *H. pylori* infections. This phenomenon controlled the inflammatory process of the intestinal tract. Altered TLR4 signaling expression and aberrant immune responses promote intestinal inflammation in patients with inflammatory bowel disease, which is closely related to the balance of the intestinal microbiota.[96] *H. pylori* spp. was significantly and positively correlated with TLR4 expression, IL-6, and TNF-α. Members of the *H. pylori* genus can activate the immune response and induce the release of pro-inflammatory cytokines by recognizing TLR4.[97]

Regulating the MAPK signaling Pathway

The mitogen-activated protein kinase (MAPK) signaling pathway is a central pathway in the eukaryotic signaling network and is involved in cell proliferation, differentiation, apoptosis, and stress response under normal and pathological conditions. MAPK refers to a group of evolutionarily conserved serine-threonine kinases, which can be divided into four subfamilies as follows: the extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinases (p38MAPK), Jun N-terminal kinase, and large mitogen-activated protein kinase 1 (BMK1, also termed ERK5), which represent the four classical MAPK pathways, respectively.[98] Zhang[99] demonstrated that the geranylgeranyl acetate in *Salvia miltiorrhiza* EOs exerts an inhibitory effect on inflammatory responses generated by intestinal mucosal injury in rats by blocking the activation-regulated p-p38MAPK protein signaling pathway. Ayman et al[100] reported that the anti-colitis mechanism of action of geraniol operates through regulating Wnt/glycogen synthase kinase-3 beta/β-catenin, p38MAPK, NF-κB, and PPAR-γ signaling pathways, thus exerting antioxidant, anti-inflammatory, and immunosuppressive effects. According to Wang et al.[101] *Boswellia serrata* EOs inhibited MAPK and NF-κB signaling pathways and improved body weight loss, diarrhea, and blood in stool in mice with DSS-induced colitis. Additionally, they reduced serum TNF-α and IL-6 levels.

Effects of the Chief Essential Oils Components on UC

Terpenes

Terpenoids, such as monoterpenes and sesquiterpenes, are the key components of secondary metabolites of plants. They are characterized by numerous structural types and biological activities.[102]

β-stilbene is a natural bicyclic sesquiterpene, which can be extracted from EOs of plants with low toxicity. Moreover, it exerts numerous pharmacological effects, including anti-inflammatory,[103] antibacterial,[104] anxiolytic,[105,106]

antitumor,[106] and antioxidant effects.[107] The intestinal symptoms of DSS-induced colitis in mice were improved by the inhibition of iron death.[108] Wu et al[109] investigated Rsl3-induced macrophage iron death in the colon of UC mice; β-stigmasterol decreased pro-iron death factors, inhibited lipid peroxidation and inflammation, and increased anti-iron death factors, suggesting its protective effect on UC.

Perillyl alcohol also termed dihydrocumyl alcohol, is a naturally occurring monocyclic terpenoid derived from the mevalonate pathway in plants. Perillyl alcohol is effective in cancer treatment, such as hepatocellular carcinoma, breast cancer, and lung cancer.[110,111] Perillyl alcohol can inhibit the proliferation and Notch-1 protein expression of colon cancer SW480 cells and downregulate the Rspo3 gene and protein expression, suggesting its use as a therapeutic agent for Rspo3 protein high-expressing colon cancers. This in turn provides a novel direction for the prevention and treatment of colon cancer.[112] Eswara Rao Puppala et al[113] demonstrated that perillyl alcohol significantly reduced the protein expression of NF-κB, STAT3, and TLR-4 in colon tissues as well as reduced the expression of TNF-α, IL-1β, IL-6, and JAK2. Additionally, it increased the levels of dopamine and 5-HT in the cerebral cortex and HP in dextran sulfate-sodium -induced UC experiments in mice. Simultaneously, it significantly reduced adrenaline levels in the cerebral cortex and HP and cortisol levels. Perillyl alcohol can be used as a novel treatment for psychological stress-induced UC.

Olive bittersweet (oleuropein, Ole) is an active ingredient extracted from the leaves of *Olea europaea*. It exerts strong antioxidant, antibacterial, and antiviral effects.[114] Giner et al[115] investigated the use of Ole in the oral treatment of DSS-induced UC mice; Ole inhibited the accumulation of neutrophils and the colonic tissue expression of matrix metallo-proteinase-9 expression as well as the ability of hydroxytyrosol (active metabolite) to reduce lipopolysaccharide-induced moderate reductions in IL-1β, IL-6, and TNF-α mRNA expression in macrophages. Ole has the potential as a therapeutic agent for UC.

1.8-eudesmus (1,8-cineole) is a natural monoterpene found in aromatic plants of the genera Eucalyptus, Rosaceae, and *Salvia officinalis*. It has an odor similar to that of camphor, good transdermal penetration, low toxicity to humans and animals, and environmental friendliness. 1.8-cineole possesses several biological and pharmacological activities, including the amelioration of pancreatitis,[116] antiproliferative and anticholesterogenic properties,[117,118] the amelioration of nonalcoholic steatohepatitis,[118] antibacterial, insecticidal, and anti-inflammatory effects. Santos et al[119] investigated the possible mechanism of action of 1.8-cineole on tissue damage in rats with 2.4,6-Trinitrobenzene sulfonic acid (TNBS) colitis; it decreased MPO activity, increased glutathione (GSH) in the colon, and exerted an anti-inflammatory effect.

The chained monoterpene carbohydrate β-laurene is an essential component of plant EOs. It is a raw material for fragrances, which can be easily obtained from turpentine, the second major component of β-pinene, by thermal cracking. β-Laurene possesses good analgesic, anti-inflammatory, and antioxidant properties. According to Almarzooqi et al[120] the administration of β-laurose in DSS-treated mice restored the colon length, decreased DAI and MPO enzyme activity, and inhibited pro-inflammatory mediators. Its mechanism of action involves the inhibition of MAPKs and NF-κB pathways to limit inflammation.

p-Cymene is a natural monoterpene present in citrus peel oil and cinnamon leaves; it is used as a flavoring agent in foods and has antioxidant and antimicrobial properties[121]. Formiga et al[122] investigated p-Cymene for the treatment of TNBS-induced colitis in rats. It reduced MPO activity in the colon, displayed antioxidant properties, lowered MDA levels, and restored GSH levels. Additionally, p-Cymene reduced IL-1β and TNF-α in serum, restored IL-10 levels in colon tissues, and downregulated NF-κB transcription, thereby reducing intestinal inflammation (Table 2).

Monophenols

Carvacrol, also termed carvacrol, is a monoterpene phenol abundant in aromatic plants; it displays strong antibacterial, anti-inflammatory, and antioxidant pharmacological and health-promoting effects with promising applications.[123] EOs of *Origanum onites L*. reduced colonic damage in 2,4,6-trinitrobenzene sulfonic acid-induced colitis, and carvacrol was identified as a major component.[74] Souza et al[124] investigated acetic acid- or other drug-induced UC mice, with oxidative damage as one of the key features. The use of carvacrol in UC treatment suppressed TNF-α and IL-1β levels and reduced oxidative damage through the increase of antioxidant enzymes in mice. These findings suggest the potential of carvacrol for UC treatment.

Muscimol, also termed thymol, has the pungent and herbaceous aroma of *Thymus* spp. It was first extracted from the EOs of muskgrass and Chenpi. Muscimol has antiseptic and bactericidal properties and is widely used in food and medicine. Medically, it is used as an antiseptic, fungicide, and liver function reagent.[125] The therapeutic benefits of muscimol have been reported in acute and chronic gastric ulcers in rats.[126] The drug prednisolone displays potent immunosuppressive properties for the treatment of UC; however, it leads to substantial adverse effects.[127] Unlike prednisolone, muscimol is a safe and natural phenol with considerable immunomodulatory capacity as well as antimicrobial and antioxidant properties.[128–130]Tahmasebi et al[131] treated acetic acid-induced UC rats using muscimol; the muscimol-treated group demonstrated strong antioxidant properties, compared with the positive drug group. Muscimolol reduced nitric oxide levels and malondialdehyde concentrations, inhibited the NF-κB pathway, and reduced IL-6, TNF-α, and IL-1β inflammatory factors.

Nerolidol is present in plants, such as orange leaves, roses, lavender, lemon, and grapefruit.[132] Either as a constituent of plant EOs or alone, nerolidol inhibits the growth of microorganisms and is safe to use.[133] González-Ramírez et al[134] reported that the administration of nerolidol ameliorated the pathological features of colitis, prevented gastric damage, and exerted an immunomodulatory effect in the oxazolone model (Table 2).

Coumarins

Bergamottin, a member of the furanocoumarin family of plant secondary metabolites, inhibits the growth of colon cancer cells[135] and blocks NF-κB signaling activation, exhibiting anti-inflammatory capacity.[136] Adakudugu et al[137] studied acetic acid-induced UC in rats; bergamottin promoted intestinal ulcer wound healing, reduced pro-inflammatory cytokine expression (TNF-α and IL-6), and decreased ROS expression, thereby reducing oxidative stress. Coumarins antagonize vitamin K, which in turn exhibits anticoagulant effects.[138] Researchers have reported a close relationship between inflammation and coagulation.[139] The anti-inflammatory effects of bergamottin in UC treatment may be attributed to its anticoagulant activity. Bergamottin is a potential alternative method for UC treatment in the future (Table 2).

Summaries and Perspectives

The incidence of UC, classified as an inflammatory bowel disease, has been increasing progressively. Patients with UC endure considerable pain and urgently require medication with minimal adverse effects and high efficacy. EOs possess aromatic properties that enable rapid therapeutic effects and targeted delivery to the affected area. Additionally, EOs exert diverse pharmacological effects, including anti-inflammatory, anti-tumor, anti-oxidant, and anti-bacterial activities, thereby demonstrating substantial potential for advancement in UC treatment. This article provides a comprehensive overview of various EOs and their potential efficacy in alleviating and managing UC through anti-inflammatory, antioxidant, antidepressant, and anti-insomnia properties as well as their ability to restore the intestinal flora balance. Notably, terpenes have emerged as the primary active constituents in UC treatment. Despite the efficacy of EOs in UC management, certain issues about the fundamental research, quality stability, and standardization of management hinder their clinical application. The majority of compound investigations on EOs were confined to in vitro studies, with limited in vivo research. Researchers should conduct additional animal experiments to substantiate their efficacy while exploring drug formulations and clinical trials for validation. EOs consumed orally have been associated with varying degrees of adverse effects. Some EOs are safe at low concentrations, whereas some exhibit toxicity at high concentrations, manifesting as lethal doses.[149] Adokoh et al[150] investigated the oral toxicity of EOs extracts of *Citrus aurantium* by using the following methods: acute toxicity single-dose and repeated-dose studies. They observed necrosis, edema, and inflammation in the liver, spleen, and kidneys through histopathological studies. Low levels of hemoglobin and high levels of liver enzymes in the subchronic phase confirmed the mild toxicity of *Melissa officinalis* EOs. The oral administration of *Melissa officinalis L*. EOs resulted caused substantial changes in mice behavior and elucidated the biochemical parameters of hepatic and renal functions.[151] When administered orally at >1 g/kg doses, different pathological changes were detected in the stomach, duodenum, liver, and kidneys. Chaihu EOs caused liver injury in rats at doses ranging from 0.19 mL/kg to 0.42 mL/kg. Additionally, the hepatocytes demonstrated irreversible changes, such as edema, steatosis, and eosinophilia.[152] The oral administration of 300 mg/kg of Croton EOs in mice for 7 days resulted in renal tubular injury, proteinuria, collagen deposition, macrophage infiltration, and nephrotoxicity.[153]

Table 2 Mechanism of Action of the Chief Active Components of Essential Oils in the Treatment of Ulcerative Colitis

Compound Name	Animal Model	Dose/Course of Treatment	Mechanisms	References
Limonene	A model of oxazolone-induced colitis	Oral administration for 7 days, 300 mg/kg	Decreased TNF-α as well as IL-5 and IL-13 Antioxidant, anti-inflammatory TGF-β and ERK1/2 signaling pathways	[12]
Linalyl acetate (LA) + sulfasalazine	Experimental colitis induced by dextran sodium sulfate in rats	Intraperitoneal injection for 5 days, 10,100 mg/kg	Reduced ACh-induced colonic contractions Tendency to lower serum IL6. Reduction of blood pressure elevation in UC rats subjected to repeated stresses	[140]
Perillyl alcohol	DSS-induced colitis in mice	Oral administration for 14 days, 100, 200 mg/kg	Perillyl alcohol reverses the TLR4/NF-κB pathway and IL-6/JAK2/STAT3 pathway by inhibiting them in isolated mouse colon and brain Inhibits oxidative stress, inflammatory response.	[113]
Nerol	A model of oxazolone-induced colitis	Oral administration for 7 days, 10, 30, 100, 177.8, 300 mg/kg	Reduced IL-13 production, TNF-α activity Prevents stomach damage and has immunomodulatory effects	[141]
1,8-Eucalyptin	TNBS induces colitis in rats	200, 400 mg/kg	Reduces MPO activity Increased glutathione (GSH)	[119]
Ice chips, thymoquinone	TNBS induced colitis in rats	Oral administration for 15 days of 0.05% thymoquinone (equivalent to an ADI of 75 mg/kg), ice chips - 0.09% and 0.18% (equivalent to 135 mg/kg and 270 mg/kg/day)	Reduced concentrations of pro-inflammatory cytokines IL-1β and IL-6	[142]
Olive amygdalin	DSS-induced colitis in mice	Oral administration for 7 days of 1% olive bittersweet	Inhibition of inflammatory cytokines and reduction of COX-2, iNOS, and MMP-9 protein expression in colon tissues NF-κB signaling pathway	[115]
Geraniol	TNBS induces colitis in rats	Oral administration for 11 days, 250 mg/kg	Antioxidant, anti-inflammatory, immunosuppressive. Regulation of Wnt/GSK-3β/β-Conjugated Protein, p38MAPK, NF-κB and PPARγ Signaling Pathways	[100]
Menthol	TNBS induces colitis in rats	Oral administration for 3 days, 20, 50, 80 mg/kg	Significantly lower levels of IL-1β, IL-6, TNF-α and MPO NF-κB signaling pathway	[11]
Patchouli alcohol	DSS-induced colitis in mice	Oral administration for 7 days, 10, 20 and 40 mg/kg	Decreased pro-inflammatory factors TNF-α, IFN-γ, IL-1β, IL-6 Increased anti-inflammatory cytokines IL-4 and IL-10 5-HT Metabolic pathway	[143]
β-Caryophyllene	DSS-induced colitis in mice	Oral administration of 30, 150, or 300 mg/kg for 7 days before DSS treatment and 7 days after DSS induction	Inhibits lipid peroxidation and inflammation Improving Iron Death in UC MAPK/NF-κB signaling pathway	[144]

(*Continued*)

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Table 2 (Continued).

Compound Name	Animal Model	Dose/Course of Treatment	Mechanisms	References
ETO-Curcumin	DSS-induced colitis in mice	Oral administration for 7 days, 5, 25 and 50 mg/kg	Reduced fecal bleeding, lower spleen weights Upregulated expression of the anti-inflammatory cytokine IL-10 Inhibition of the chemokine CCL17	[145]
Carvacrol	Acetic acid-induced colitis in mice	Oral administration of 5, 50 and 100 mg/kg for 3 days prior to acetic acid induction	Inhibition of TNF-α and IL-1β Reduced oxidative stress, antioxidant Reduced abdominal pain sensation in rats	[124]
Thymol muscimol	Acetic acid-induced colitis in rats	Oral administration for 10 days, 100 mg/kg	Inhibits inflammation, reduces oxidative stress, antioxidant NF-κB signaling pathway	[131]
Bergamottin	Acetic acid-induced colitis in rats	Oral administration for 5 days, 3, 10 and 30 mg/kg	Reduced damage to the colon and degranulation of mast cells NF-κB signaling pathway	[137]
Isoegomaketone	DSS-induced colitis in mice	Oral administration for 5 days, 1.5 mg/kg	May reduce levels of inflammatory cytokines	[146]
Atractylone	DSS-induced colitis in mice	Oral administration for 10 days, 50 mg / kg	Anti-inflammatory, anti-oxidative stress, intestinal damage repair Inhibition of the expression of pro-inflammatory cytokines IL-6 and TNF-α PI3K-AKT signaling pathway	[147]
p-Cymene	TNBS induced colitis in rats	Oral administration, 25, 50, 100 and 200 mg/kg	Antioxidant, anti-inflammatory and immunomodulatory effects Cells that can protect the pre-epithelial barrier or epithelial barrier	[122]
β-Myrcene	DSS-induced colitis in mice	Oral administration for 7 days, 50 and 100 mg/kg	Good anti-inflammatory effect can modulate MAP kinase and down-regulate NF-κB pathway repressor	[120]
β-Caryophyllene	Oxazolone-Induced Colitis	Prophylaxis was administered orally for 7 days at 12.5, 25, or 50 mg / kg, and after induction, 50 mg / kg was administered orally for 3 days	Reduced activation of ERK1/2, p65 NF-κB, IKKα/β, CREB, caspase-3 and Ki-67 Reduced levels of CXCL1/KC, TNF-α and MIP-2 NF-κB/PPARγ signaling pathway	[148]

First, researchers should achieve a comprehensive understanding of the toxic effects of EOs, elucidate the underlying toxic substances, toxic processes, and mechanisms of action, establish relevant quality standards, or utilize contemporary preparation techniques to effectively regulate the quality and stability of EOs. Furthermore, enhancing the management of EOs is crucial. From a clinical perspective, clinicians should judiciously select the appropriate route of administration, rigorously control the dosage or purity, and carefully consider the applicable population to mitigate the potential risks. Research on the safety of EOs is long-term and extensive and can provide a more reliable basis for the use of drugs and healthcare. Different EOs have varying degrees of toxicity, and the cross-dose between the efficacy dose and the toxicity dose has not yet been explored.

Second, most studies on pharmacological activity are based on EOs that have not been isolated and purified; the complex chemical composition leads to the selection of EOs for UC treatment. Nonetheless, their mechanism of action has not been elucidated. Terpenoids are the key EOs components and are effective against diseases, such as artemisinin, an anti-malarial sesquiterpene, and cyclic sesquiterpene chamomile lactone, with anti-Leishmania amazonensis activity against malaria. Chamomile lactone, the cyclic sesquiterpene, works against Amazonian Leishmania protozoa. Therefore, researchers should investigate the pharmacological effects of terpenoids in plant EOs, particularly the complex and diverse structure of sesquiterpenes. Additionally, they should explore whether the different types of carbon skeletons correspond to different pharmacological activities.[154]

The pharmacological effects of EOs on UC are focused on evaluating their antibacterial, antioxidant, and anti-inflammatory functions. Additionally, preliminary explorations of EOs compounding in anti-UC studies have provided ideas for the identification of novel pharmacological functions. Plants consist of numerous active EOs with characteristic components; however, their application is limited and has not been exploited. Therefore, researchers should explore the following four areas: (1) EOs and their individual compounds to determine the pharmacological effects and mechanism of action, analysis of the internal effective component groups, and individual components of the pharmacodynamic function; (2) varying synergistic effects of EOs, the efficacy of traditional Chinese medicine through histological research, the study of a single flavor, drug pairs or a combination of drug components, the content of changes and the mechanism of change, and the new pharmacological and pharmacodynamic effects of the drug; (3) because of the relative safety, reliability, and efficiency, EOs in the field of food application research, rational selection in the development of natural spices, natural antiseptic preservatives, the development of spices, and composite preservatives warrant research; (4) considering the differences in origin, parts, and extraction methods of different EOs, researchers should investigate the cultivation standards, medicinal standards, and safety of medicinal herbs, establish scientific evaluation methods, and guide their rational use. These steps will help them promote the development and research on EOs as well as their comprehensive application and industrialization.

In conclusion, this article presents a review of the existing EOs and their active ingredients, which will facilitate the treatment of UC and drug development.

Abbreviations

UC, Ulcerative colitis; EOs, Essential oils; IBD, inflammatory bowel disease; NF-κB, nuclear factor kappa-B; TNF-α, tumor necrosis factor; IL-6, Interleukin-6; IL-1β, Interleukin-1β; PPARγ, peroxisome proliferators-activated receptors; MPO, myeloperoxidase; SCFA, short-chain fatty acids; TLR4, Toll Like Receptor 4; NLRP3, Nucleotide- binding oligomerization domain, leucine- rich repeat and pyrin domain- containing 3; ROS, reactive oxygen species; NO, nitrous Oxide; DSS, dextran sulfate sodium salt; TNBS, trinitro-benzene-sulfonic acid; DAI, disease activity index; NOS, nitric oxide synthase; DNCB, 2, 4-dinitrochlorobenzene; 5-HT, 5-Hydroxytryptamine; MMP-9, Matrix metalloproteinase-9; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; SOD, super oxide dismutase; 8-OHdG, 8-hydroxydeoxyguanosine; GSH-Px, glutathione peroxidase.

Data Sharing Statement

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

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Disclosure

The authors report no conflicts of interest in this work.

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