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Naringenin and Herbal Management of Ulcerative Colitis: A Review

Ziyaurrahman A.R.*, Prasad Shewale, Yogesh S. Ahire, Pratiksha S. Shewale and Nayan K. Raut

K. B. H. S. S. Trust's Institute of Pharmacy and Research Centre, Bhayegaon, Malegaon, Nashik, Maharashtra, India

**Corresponding Author*

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Abstract: Ulcerative colitis (UC) and Crohn's disease are chronic inflammatory conditions of the gastrointestinal (GI) tract, collectively known as inflammatory bowel disease (IBD). Nonsurgical colitis includes ulcerative proctitis, proctosigmoiditis, left-sided colitis, and pancolitis. Studies on herbal therapy for IBD published in Medline and Embase were reviewed and reported on treatment response and remission rates. Naringenin is a flavonoid found in many plants and has been used to treat inflammation since it was discovered to have nutritional benefits. Naringenin has been shown to have a protective effect in animal models of ulcerative colitis, but the mechanism remains unclear. This article emphasizes the use of naringenin as an anti-inflammatory and anti-infective agent and as an adjunctive prophylactic agent for the treatment of various inflammatory, infectious diseases and various herbal medicines for management of Ulcerative colitis.

Keywords: Ulcerative colitis, Flavonoid, Naringenin, Inflammatory Bowel Disease, Herbal medicine

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Introduction

Chronic inflammatory conditions of the gastrointestinal (GI) tract known as inflammatory bowel disease (IBD) include ulcerative colitis (UC) and Crohn's disease. Albeit the etiology remains to a great extent obscure, hereditary helplessness factors and the enactment of the mucosal resistant framework in light of normal luminal bacterial antigens and ongoing obsessive cytokine creation add to the commencement and route of IBD (Podolsky, 2002; Baumgart and Carding, 2007; Liu *et al*., 2009). The annual incidence of ulcerative colitis (UC) ranges from about 10 to 20 cases for every 100,000 individuals, while its prevalence in Western nations is estimated to be between 100 and 200 cases per 100,000 people (Gasche *et al*., 2000; Card *et al*., 2003; Loftus, 2004). Nonetheless, there are a few distinctions in the clinical qualities of UC in China, and populace based epidemiological examinations are expected to decide the pervasiveness and frequency (Wang

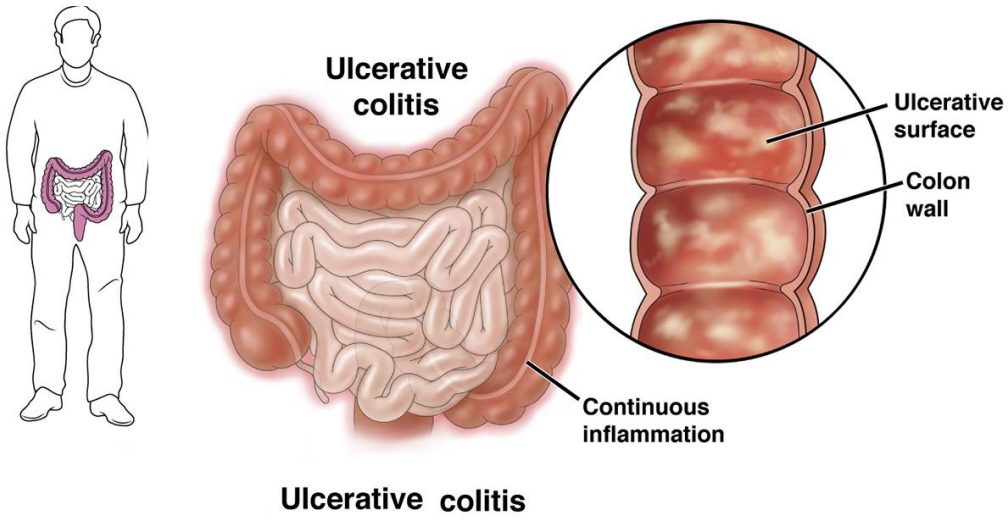

Fig. 1: Ulcerative colitis (Inflammatory bowel disease).

and Ouyang, 2007). China has seen a significant rise in the number of UC patients over the past ten years; lesions are more prevalent on the left side, men and women are equally affected; smoking has a positive relationship with disease severity; and family members are rarely involved[7]. Proof has shown that low adherence is a huge boundary to the effective administration of UC patients (Kane, 2006). Just 40%-60% of patients with recently analyzed or well established UC respond treatment (Kane *et al*., 2001; Sewitch *et al*., 2003; Carveny *et al*., 2007). Consequently, improving medication adherence has become one of the most important steps in effective disease management.

Until this point in time, a few mitigating drugs have been utilized in the treatment of UC, including 5-aminosalicylate, azathioprine, 6-mecaptopurine, cyclosporine, and monoclonal antibodies. The fundamental objective of clinical treatment for UC patients is focused on the acceptance and ensuing control of side effects and mucosal irritation to furnish a better personal satisfaction with negligible steroid openness (Yadav and Liu, 2009).

Symptoms of UC:

Symptoms of ulcerative colitis can vary depending on the severity of inflammation and where it occurs. Signs and symptoms may include: Diarrhea, often with blood or pus, rectal bleeding – loss of small amount of blood in the stool, abdominal pain and cramping, abdominal pain, insomnia, inability to escape even urgently, weight loss, fatigue, fever, Developmental delays or growth-related concerns in children; and most people with ulcerative colitis have moderate symptoms. The route of non-surgical colitis can vary, and some people can go for a long time which is called remission (Kane *et al*., 2001; Yadav and Liu, 2009; Hoivik *et al*., 2013).

Type of UC:

Health care providers often classify ulcerative colitis based on its location (Fig. 1). The symptoms of each type often overlap. Types of nonsurgical colitis include (Torres *et al*., 2012; Peyrin-Biroulet, 2012):

- *Ulcerative proctitis*: An abscess in the area closest to the anus, called the rectum. Rectal bleeding may be the only symptom of the disease.
- *Proctosigmoiditis*: Inflammation of the lower end of the intestine involving the rectum and sigmoid colon. Symptoms include bloody diarrhea, abdominal cramping and pain, and the inability to have a bowel movement despite the urge. This is called tenesmus.
- *Left-sided colitis*: Inflammation extends from

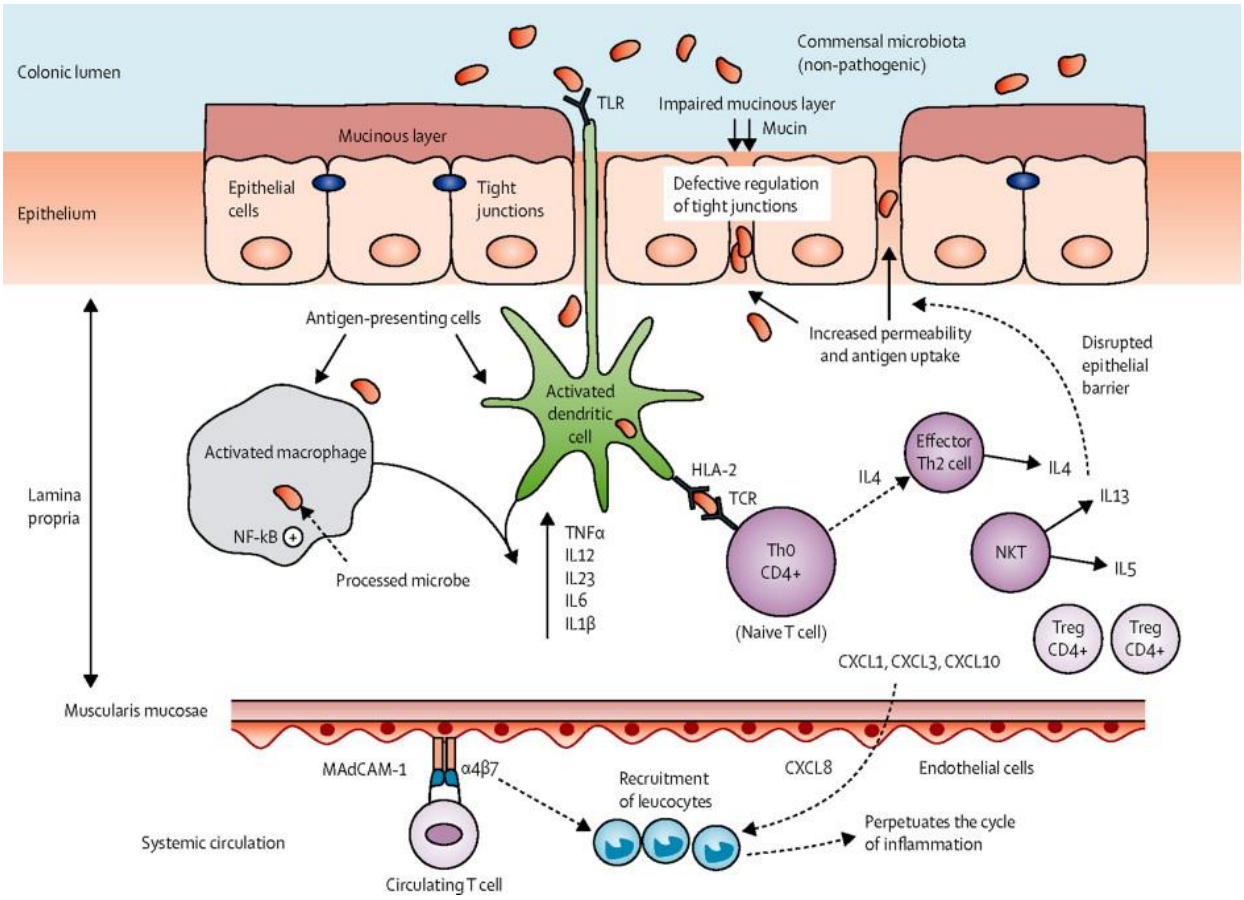

Fig. 2: Physiology of Ulcerative colitis.

the rectum to the sigmoid and descending colon. Symptoms include bloody diarrhea, abdominal and left-sided pain, and an urge to defecate.

- *Pancolitis*: Affects the entire intestine and causes severe, bloody diarrhea with abdominal pain and cramping, fatigue, and a significant loss of appetite.

Pathophysiology of Ulcerative Collitis:

Although the existing literature often describes the pathogenesis of ulcerative colitis alongside Crohn's disease, there are important differences. An overview of intestinal immunity in healthy subjects and during ulcerative colitis is shown in Figure 2. Colonic epithelial cells (colonocytes) have a strong barrier function and epithelial barrier defects in the pathogenesis of ulcerative colitis. Expression of peroxisome proliferator-activated receptor gamma (PPAR-γ), a negative regulator of NF-κB-dependent inflammation, is decreased in colonocytes of patients with ulcerative colitis, suggesting a causal link (Jiang *et al*., 1998; Dubuquoy *et al*., 2003). Existing PPAR-1 agonists are limited by cardiac and metabolic toxicity. However, a 5-aminosalicylic acid (5-ASA) analog with greater PPAR-γ agonist activity was developed (Rousseaux *et al*., 2005). Auto-antibodies against colonocyte-associated tropo-myosin have been described in ulcerative colitis, but there is little convincing evidence to identify ulcerative colitis as an autoantibody-associated disease. Colonocyte-associated defects in X - box binding protein 1 (XBP1), a key component of the endoplasmic reticulum stress pathway, have been shown in ulcerative colitis (Kaser *et al*., 2008).

Alterations in the proliferative factor, a family of intracellular proteins that are produced in response to mucosal injury and contribute to the integrity of the mucosal barrier, have been described in patients with ulcerative colitis (Podolsky and Isselbacher, 1984; Mashimo *et al*.,

1996). The argument that a defect in barrier function is a key driver of the disease is supported by the deterioration of intestinal goblet cells and the permeable mucus barrier in patients with active ulcerative colitis (Johansson *et al*., 2014).

Dysbiosis occurs in patients with ulcerative colitis, although at a lower rate in patients with Crohn's disease (Andoh *et al*., 2011). A decrease in flora with a low number of Firmicutes and an increase in Gamma-proteobacteria and Entero-bacteriaceae were observed in patients with ulcerative colitis (Frank *et al*., 2007). In addition, patients with this disease overexpress sulfite-reducing Deltaproteobacteria in the intestine (Roediger *et al*., 1997). However, it is unclear whether dysbiosis is a cause or a consequence of mucosal inflammation.

Toll-like receptor 2 (TLR2) and Toll-like receptor 4 (TLR4) are increased in colonocytes and lamina propria in active ulcerative colitis, but it is not clear whether increased expression is the cause or consequence of mucosal inflammation (Hausmann *et al*., 2002). Similarly, TLR4 polymorphisms have been reported in patients with ulcerative colitis and Crohn's disease, but their role in the pathogenesis of the disease is unknown (Senhaji *et al*., 2014). Activated neutrophils accumulate in the blood and intestinal tissue of patients with active ulcerative colitis compared with normal volunteers (Hanai *et al*., 2004). In patients with ulcerative colitis, dendritic cells have increased expression of costimulatory molecules and are likely to be the first responders of barrier integrity (Hart *et al*., 2005).

Neoplastic lymphoid cells (ILCs) may be central to the pathogenesis of inflammatory bowel disease. ILC3 is a key mediator of chronic intestinal inflammation (Buonocore *et al*., 2010). Furthermore, ILCs isolated from patients with active ulcerative colitis showed increased gene expression of key ILC3 cytokines (IL17A and IL22), transcription factors and cytokine receptors (including IL23R) (Geremia *et al*., 2011). The possibility that ILCs are drivers of disease pathogenesis has led to new therapeutic targets.

Although high concentrations of IgM, IgA, and IgG have been reported in inflammatory bowel disease, there is a disproportionate increase in IgG1 antibodies in patients with ulcerative colitis. It is unclear whether B cells are drivers of disease pathogenesis or merely respond to barrier disruption (Fuss *et al*., 1996; Geremia *et al*., 2011).

Current evidence points to innate and adaptive cellular immunity as key to disease pathogenesis. Previous evidences suggest that ulcerative colitis is a transformed T-helper-2 (Th2) disease, while Crohn's disease is Th1. In support, interleukin-5 (IL-5)-producing Th2 polarized T cells have been found in the colonic lamina propria of patients with ulcerative colitis (Fuss *et al*., 1996). In addition, IL-4 and IL-13 mRNA levels were significantly increased in rectal biopsies of patients with ulcerative colitis compared with patients in the control group (Inoue *et al*., 1999). Further data has implicated IL-13 in the pathogenesis of ulcerative colitis. IL-13, produced by non-classical natural killer T cells (probably members of the ILC family), is a key mediator of epithelial cytotoxicity and barrier dysfunction in ulcerative colitis (Fuss *et al*., 2004; Heller *et al*., 2005).

The development of the T-helper Th1/Th2 paradigm for Crohn's disease and ulcerative colitis was further expanded by 2014 data, which revealed a new population of IL-9-producing CD4-positive cells. Th cells was identified and contributed by the transcription factor PU1 development of ulcerative colitis (Gerlach *et al*., 2014). Th9 cells develop after undifferentiated Th (Th0) cells encounter the MHC class II antigen complex in the presence of the cytokines transforming growth factor β and IL-4. IL-9 produced by Th9 cells inhibits cell proliferation and repair and negatively affects intestinal barrier function. In addition, IL-9 modestly but

significantly increases the concentration of tissue tumor necrosis factor-TNF-α.

Naive lymphocytes are impressed when activated by a specific trafficking program. Dendritic cells play a key role in this process by integrating environmental cues and expressing specific integrins and chemokine receptors. For example, dendritic cells residing in Peyer's patches or the intestine from lymph nodes to produce the vitamin retinoic acid and induce β4β7 integrin and C-C chemokine receptor type 9 (CCR9) expression in T and B lymphocytes. Therefore, imprinted cells enter the circulation and, after reentering the intestinal vasculature, attract appropriate ligands-MAdCAM-1 (for α4β7) and Chemokine (C-C motif) ligand 25 (CCL25) (for CCR9). Although mucosal defects have not been demonstrated in non-surgical colitis patients, therapeutic strategies targeting the interaction of α4β7 with MAdCAM have become key tools in the management of ulcerative colitis (Feagan *et al*., 2013).

Herbal Medicines:

Herbal medicine refers to folk and traditional medicinal practices based on the use of plants and plant extracts to treat medical conditions. The use of herbs to treat ailments is almost universal among the local population. At the end of the 20th century, several traditions came to dominate the practice of herbal medicine in the West. Herbal medicine is one of the most common traditional Chinese medicine (TCM) methods. 28.9% of US adults regularly use one or more traditional Chinese medicine therapies, with 9.6%-12.1% taking the form of herbal products (Comar and Kirby, 2013). Recent studies have shown that the percentage of adults using TCM therapy for GI symptoms is between 20% and 26%, but patients with functional GI disorders are more likely to use it, such as those with chronic GI conditions (Tillisch *et al*., 2007; D'Inca *et al*., 2007).

The use of complementary medicine among IBD patients, especially in the form of herbal therapy, is widespread in the Western world and in many Asian countries such as China and India (Langmead *et al*., 2004). Although there are only a few controlled trials on the efficacy or safety of these natural products, their use appears to be increasing. So far, there is limited controlled evidence showing the effectiveness of TCMs such as *Aloe vera* gel, wheatgrass juice, *Boswellia serrata*, and fennel root in the management of UC patients (Langmead *et al*., 2004).

Flavonoids:

Naringenin:

Plants produce many natural products, including phenolic compounds, which are responsible for the main organoleptic properties of foods and beverages derived from plants. They play an important role in the color and flavor characteristics of fruits and vegetables (Horvath, 2005; Tapas *et al*., 2008).

Flavonoids, a group of phytochemicals, have a variety of beneficial biochemical and pharmacological properties and are mainly of plant origin such as fruits, vegetables, tea, wine, seeds, herbs, spices and whole grains (Hughes *et al*., 2008). Flavonoids are biological pigments responsible for the red-blue color in flowers, fruits, and leaves (Erdogdu *et al*., 2009).

Flavonoids are a major class of plant secondary metabolites that have many functions, including pigmentation and antioxidant activity. Flavonoids are synthesized from phenylpropanoid derivatives by condensation with malonyl CoA. For example, the condensation of p-coumaroyl-CoA (C6-C3) and three molecules of malonyl-CoA (C3) produces naringenin chalcone, a diphenylpropane unit (C6-C3-C6) that is converted to naringenin (Fig. 3) by flavone phenylchromene-4-one) conjugate backbone and ring closure. These modifications further produce different structural forms such as chalcones, flavanones, dihyroflavonols and flavans, anthocyanins, flavones and flavonols, and isoflavonoids (Li-Tao *et al*., 2010).

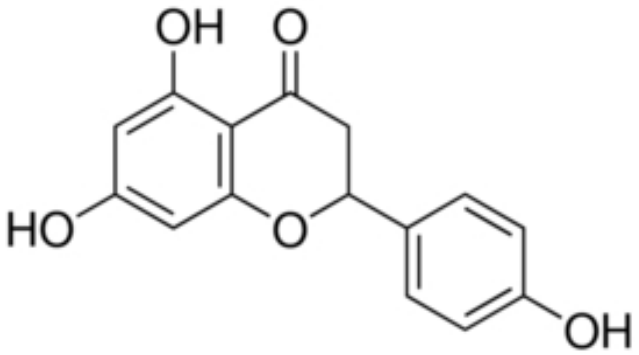

Fig. 3: Structure of Naringenin.

Naringenin (4,5,7-trihydroxy flavonone) is a flavonoid commonly found in oranges, tomatoes, cherries, and cocoa (Jain *et al*., 2011). Several pharmacological studies revealed its effects, including antidiabetic, antiatherogenic, anti-depressant, immunomodulatory, antitumor, DNA protective, hypolipidemic, and peroxisome proliferator-activated receptor activator (Lisa *et al*., 1999; Jain *et al*., 2011). It has also been shown to have some antioxidant and anti-inflammatory potential (Ines *et al*., 2009; Alam *et al*., 2014).

Naringenin has great potential to promote the recovery of DSS-treated ulcerative colitis (UC) rats by promoting intestinal epithelial injury repair, inhibiting the expression of TNF-α in intestinal epithelial cells, and promoting M1-type conversion of macrophages in intestinal tissue swelling (Vaishnava, 2005). Naringenin has been shown to limit microscopic anatomical inflammation by inhibiting the TLR4/NF-κB signaling pathway, reducing the effects of inflammatory cytokine production, and regulating inflammatory mediators. In conclusion, modify-cation of these inflammatory factors significantly improved the symptoms of intestinal inflamma-tion in ulcerative colitis mice (Chu *et al*., 2013). It has been found that naringenin significantly increased intestinal absorption and up-regulated the expression of claudin-2, occludin and ZO-1 in colon tissue (He *et al*., 2009; Azuma *et al*., 2013). It has also been reported that naringenin alleviated the symptoms of colitis by reducing oxidative stress, suggesting that naringenin may be a new natural herbal product for the treatment of ulcerative colitis (Al-Rejaie *et al*., 2023).

Naringin:

Naringin is an important flavonoid in Rutaceae grapefruit fruit or peel that contributes to the bitter taste of orange juice (Li *et al*., 2018). Naringin is known for its many biological activities that have remarkable therapeutic roles and is known for its anticancer activity (Zhang *et al*., 2018), antimicrobial potential, and anti-inflammatory activity (Sui *et al*., 2018). Naringin significantly attenuated dextran sodium sulfate (DSS)-induced intestinal inflammatory symptoms, such as disease activity index (DAI), intestinal contraction, and intestinal pathological lesions (Cao *et al*., 2021). Naringin was found to significantly attenuate DSI-induced intestinal inflammatory markers, including disease activity index (DAI), shortened intestinal length, and pathological damage by reducing inflammatory cytokines and oxidative stress. Neringin reduced the secretion of inflammatory factors and increased the expression of tight junction proteins in the intestinal tissue, ameliorated the intestinal flora disorder induced by DSS, and improved intestinal health in mice. Therefore, Naringin significantly improves the pathogenic symptoms of ulcerative colitis by suppressing the inflammatory response and regulating the intestinal flora. Another study investigated the mechanism of Naringin in mice induced with two types of ulcerative colitis by dextran sodium

sulfate (DSS) and Trinitrobenzene sulphonic acid (TNBS) (Dong *et al*., 2021). It was also concluded that Naringin significantly changed the symptoms of colitis, reduced inflammation, reduced oxidative stress and apoptosis of intestinal epithelial cells. Furthermore, Naringin can activate PPAR-γ signaling pathway and inhibit NF-κB pathway and MAPK pathway to prevent colitis in mice, suggesting that Naringin can be used as a natural therapeutic agent for treatment and nutritional improvement; gut microbiology in ulcerative colitis patients.

Effect of Naringenin on Acetic Acid-Induced Ulcerative Colitis:

Previous studies have shown that naringenin administration effectively protects gastric lesions and ulcers (Parmar, 1990; Motilva *et al*., 1994). Protection against experimental UC induced by naringenin (NG) was accompanied by the restoration of intestinal thickening, an indirect assessment of intestinal inflammation. Micros-copic scores of histopathological sections confirmed the protective effect of NG, as intestinal tissue injury, necrosis, and inflammation were reduced in a dose-dependent manner. It has been observed that NG treatment enhances the production of gastric mucus in rats subjected to absolute ethanol. Moreover, naringenin appears to counteract the reduction of intestinal mucus linked to NG treatment. This protective activity can be attributed to its antioxidant and anti-inflamma-tory properties (Motilva, 1994).

Oxidative stress plays an important role in the initiation and progression of IBD (Kruidenier and Verspaget, 2002). Animal experimental colitis is characterized by oxidative damage and an imbalance between oxidant and antioxidant substances (Droge, 2002). AA-induced colitis model induces vascular dilatation and leukocyte aggregation, as well as increased blood flow, leading to increased oxygenation and thus overproduction of free radicals and ROS (Closa and Folch-Puy, 2004; Hartmann *et al*., 2012). Several studies have shown that free radicals play an important role in the pathogenesis of mucosal injuries (Yoshikawa *et al*., 1989; Isozaki *et al*., 2006). Additionally, free radicals and ROS have been reported in ulcerative colitis colorectal specimens (Ademoglu *et al*., 2004; Bitiren *et al*., 2010). The first line of the oxidative defense system against free radicals is the sulfhydryl group in the GSH or NP-SH peptide. It is widely distributed in all biological tissues and functions as a non-enzymatic antioxidant. GSH inhibits the oxidative damage of ROS through its sulfhydryl group and indirectly acts as a cofactor or coenzyme in the detoxification process of ROS enzymes (; Sivaprasad *et al*., 2002; Sivaprasad *et al*., 2004). Another aspect of the oxidative defense system is the enzymatic antioxidant. Examples of important antioxidant enzymes are SOD, CAT and GPx (Boots *et al*., 2008). Oxidative damage to cells is indicated by the levels and activity of both enzymatic and non-enzymatic defense mechanisms. in the intestines of AA-treated animals. In addition, free radicals are known to attack the lipid content of cell membranes, leading to activation of the lipid peroxidation (LPO) process and cellular damage. Therefore, the concentration of LPO-specific products such as thiobarbituric acid reactive substance (TBARS) increased, and macro- cellular important- and micromolecules such as nucleic acid and total protein decreased, indicating cellular oxidative injury and cytotoxicity. These results, in accordance with previous findings, indicate that AA exerts a detrimental effect on cellular macromolecules and impairs mucosal regeneration by disrupting the integrity of epithelial cells (El-Abhar *et al*., 2008; Cetinkaya *et al*., 2006).

Naringenin was able to improve AA-induced oxidative damage and intestinal tissue injury, confirming its potent antioxidant and anti-inflammatory properties. Previous studies found that naringenin significantly increased anti-oxidant markers such as GSH, NP-SH levels, and SOD and CAT activities (Jain *et al*., 2011; Han *et al*., 2012; Wang *et al*., 2012). Inhibition of NG can increase the activity of the antioxidant enzyme GPx, indicating the ability of NG to enhance the

effect of oxidative stress to reduce the level of lipid peroxides and prevent the formation of free radicals during the LPO process (Han *et al*., 2012; Wang *et al*., 2012). Naringenin treatment significantly ameliorated the decrease in nucleic acid and total protein in the intestinal tissue, demonstrating the cytoprotective properties of naturally occurring flavonoids. The antioxidant activity of NG mainly depends on the presence of B-ring catechol groups, which can stabilize radical species by donating hydrogen (H^+) (Jain *et al*., 2011).

Inflammatory cytokines are known to play an important role in the modulation of the mucosal immune system, where neutrophils and macrophages cause epithelial integrity and intestinal injury (Grisham and Yamada, 2012). The pathogenesis of UC is characterized by the migration of granulocytes and other leukocytes into the inflamed mucosa and superficial lesions, which secrete TNF-α, IL-6, and IL-1β (Grisham, 1994; Pavlick *et al*., 2002). The high levels of intestinal TNF-α, IL-6, and IL-1β in the AA-treated group were evidence of epithelial cell necrosis, edema, and neutrophil infiltration, which was supported by histopathological findings. These results are consistent with previous experimental and clinical studies (Popov *et al*., 2006; Stucchi *et al*., 2006; Tahan *et al*., 2011). Increased colonic PGE2 levels in the AA animal group is in agreement with Otani *et al*. (2006), where high levels of PGE2 are associated with over-production rather than decreased metabolism, both mediated by pro-inflammatory cytokines. Naringenin has been found to maintain the level of inflammatory cytokines such as TNF-α, IL-6 and IL-1β (Raso *et al*., 2001). The anti-inflammatory properties of naringenin have been suggested to be through several mechanisms, including increased phosphorylation of extracellular signal regulated kinase 5 (ERK 5) and p38 mitogen-activated protein kinase (P38 MAPK), and inhibition of NF-κB and activator protein-1 signaling (Bodet *et al*., 2008; Yang *et al*., 2011). In addition, naringenin, present in high concentrations in citrus fruits, inhibits NF-κB activation, leading to up-regulation of NF-κB downstream genes such as iNOS and COX-2 expression (Park *et al*., 2012). This enzyme catalyzes the oxidative stress-induced production of NO and prostaglandins, which are known to be important inflammatory mediators in the pathogenesis of colitis. Naringenin treatment caused a significant increase in PGE2 and NO levels in the rat intestine (Hämäläinen *et al*., 2007).

Herbal Medicines for Management of Ulcerative Colitis:

Curcuma longa:

Curcumin is an active polyphenol extracted from the root of *Curcuma longa*, a plant in the ginger family. It has been used in Traditional Chinese Medicine (TCM) and Ayurveda for centuries, and in the US it is approved by the Food and Drug Administration (FDA) as a food additive for cooking (Langhorst *et al*., 2015; Sadeghi *et al*., 2020; Banerjee *et al*., 2021). Several laboratory studies and murine colitis model studies have demonstrated antioxidant, antibacterial, anti-inflammatory and anti-cancer effects of curcumin. Important anti-inflammatory mechanisms include nuclear factor kappa light chain enhancer (NF-κB) upregulation in activated B cells, which play a key role in the development of ulcerative colitis by increasing the transcription of proinflammatory cytokines and removes intestinal obstruction. Curcumin has also been shown to improve intestinal barrier function through changes in the microbiome by regulating tight junction proteins, increasing antioxidant enzyme activity, and increasing anti-inflammatory short-chain acid-producing acid bacteria (Jabczyk *et al*., 2021).

Four studies examining the oral cavity support its use as adjunctive therapy for the induction of clinical remission in active ulcerative colitis. Long (2022) showed that treatment with 3 g oral curcumin significantly improved clinical improvement, and endoscopic response in mild-to-moderate ulcerative colitis patients receiving

mesalamine compared with placebo. Similarly, Masoodi *et al*. (2008) studied curcuminoid and mesalamine nanomicelles and reported reductions in bowel urgency scores, namely Simple Colitis Clinical Activity Index (SCAI) scores and patients' self-reported health status, whether or not oral mesalamine was administered if not. None were present before the study (Masoodi *et al*., 2008). Sadeghi et al. (2020) reported that although there is a significant difference in educational attainment between groups, clinical response rates and clinical improvement in patients receiving oral curcumin was reduced compared to placebo in patients receiving a fixed dose of ulcerative colitis medication and decreased ESR levels and improved IBDQ-9 scores (Sadeghi *et al*., 2020).

Indigo naturalis:

Indigo naturalis (IN), also known as king dye, is a dried pigment extract obtained from various plants as *Indigofera tincture* and commonly used in TCM for inflammatory diseases such as UCM. The anti-inflammatory, antioxidant, and mucosal protective effects of IN are thought to involve regulation of NFκB and mitogen-activated protein kinase (MAPK) expression, modulation of Th1- and Th2-mediated immunity, and inflammatory cytokines (IL-6). The main components involve managing TNF-α production, minimizing reactive oxygen species (ROS), and modifying nitric oxide (NO) levels (Ozawa, 2020).

Aloe vera:

A large amount of gel extracted from the leaf sap of the perennial plant *Aloe vera* (*Aloe barbadensis* Miller) has been used medicinally in Indian, Chinese, Egyptian, and European cultures to treat digestive disorders, skin lesions, osteoporosis, and cancer (Sánchez *et al*., 2020). The antioxidant and anti-inflammatory properties of *Aloe vera* are mainly attributed to anthraquinones such as aloe emodin and aloin C-glycoside, which have peroxyl radical scavenging activity. *Aloe vera* is thought to improve intestinal barrier function by stimulating mucus secretion and increasing the thickness of the mucosal layer, reducing intestinal inflammation and tissue damage (Shi *et al*., 2021). Compared oral *Aloe vera* gel with placebo in a 2:1 ratio in patients with mild to moderate ulcerative colitis. Although the mean SCCAI and histological scores were reduced in the treatment group, the rates of clinical improvement, and sigmoidoscopy improvement were not statistically significant (Langmead *et al*., 2004). Similarly, A significant reduction in disease activity index (DAI) scores was observed in 10 patients treated with daily *Aloe vera* gel enemas and oral mesalamine, but not in the placebo group (Pica *et al*., 2021).

Arthrospira platenesis:

Arthrospira platensis, also known as Spirulina, is a blue-green microalga with antioxidant properties that is a natural source of vitamins (vitamin B12 and vitamin A), minerals and phytochemicals (carotenoids and phycocyanins) (Moradi *et al*., 2021). A murine colitis study showed that treatment with spirulina reduced DSS-induced damage, decreased ROS, increased antioxidant enzyme activity, and modulated gut microbiota (Wang *et al*., 2022).

Moradi *et al*. (2021) evaluated the effects of spirulina capsules on anthropometric indices, mood, sleep, and quality of life in mild to moderate ulcerative colitis patients receiving conventional treatment. No significant effect was observed for anthropometric parameters such as body mass index (BMI) and blood pressure. Quality of life improved significantly in both treatment and control groups with decreases in sleep disturbance and stress scores during the study, but there were significant differences in quality of life and stress scores between groups at the end of the study (Moradi *et al*., 2021).

Green Tea:

Green tea (*Camellia sinensis*) leaves are rich in polyphenols and catechins such as epigallocatechin-3-gallate (EGCG), which are believed to have antioxidant, anti-inflammatory and anti-cancer effects (Barbalho *et al*., 2019). The anti-inflammatory effect of EGCG is

associated with inhibition of NF-κB, reduction of inflammatory cytokines, and increased expression of tumor growth factor T (TGFβ) (Oz *et al*., 2013).

In a study by Dryden *et al*. (2013) participants with mild to moderate UC received low-dose polyphenol E 200 mg orally or high-dose polyphenol E 400 mg twice a day in a ratio of 4:1 to receive treatment or placebo. The clinical response rate and clinical recovery rate were 66.7% and 53.3% in the combined intervention group and 0% in the placebo group, respectively (Dryden *et al*., 2013).

Flaxseed:

Flax (*Linum usitatissimum*) is grown as a food crop and is considered a functional food due to its soluble fiber, alpha-linolenic acid (ALA) and phytoestrogens. Flaxseed oil is rich in antioxidants, polyphenols, and omega-3 polyunsaturated fatty acids (PUFA), including ALA, a precursor of eicosapentaenoic acid (EPA). A study of intestinal mucosal biopsies from ulcerative colitis patients showed higher levels of arachidonic acid and lower levels of ALA and EPA in the inflamed mucosa compared with controls. Omega-3 PUFAs inhibit the conversion of arachidonic acid to pro-inflammatory eicosanoids (prostaglandins, leukotrienes, etc.) and activate the pro-inflammatory transcription factor peroxisome activator receptor (PPAR)-γ (Barbalho *et al*., 2016). ALA has been reported to reduce inflammatory cytokine production, NFκB activation, and intestinal permeability (Hassan *et al*., 2010).

Olive Oil:

Extra virgin olive oil (EVOO) is a staple of the Mediterranean diet and contains beneficial compounds such as oleuropein, hydroxytyrosol, oleocanthal and flavonoids, which have antioxidant, anti-inflammatory and anti-cancer properties. Olive oil polyphenols scavenge ROS, reduce iNOS expression, reduce angiogenesis, and reduce inflammation by reducing PPARγ and NFκB activation and inflammatory cytokine production. Treatment of human intestinal mucosal biopsies from ulcerative colitis patients with oleuropein reduced inflammatory infiltrates, resolved focal cryptitis, and regenerated goblet cells (Morvaridi *et al*., 2020).

Using a randomized, single-blind crossover trial, Morvaridi *et al*. (2020) investigated the effect of EVOO consumption on standard treatment in active and remission UC patients. Subjects consumed 50 ml of EVOO daily for 20 days, followed by a 14-day washout, followed by 20 days of CO2 exposure, or 20 days of CO_2 exposure followed by the administration of 50 ml of canola oil (CO) daily a 14-day washout, and 20 days. of EVOO consumption. Although the change in the Mayo score was not significant, the score of gastrointestinal symptoms, ESR and hs-CRP levels were significantly higher (Morvaridi *et al*., 2020).

Saffron:

Saffron is a culinary spice that grows from the stigma of the *Crocus sativus* plant that grows in the Mediterranean and Asia. Saffron is believed to have several therapeutic effects, including memory-enhancing, antidepressant, anti-inflammatory, and anti-inflammatory effects related to its main bioactive compounds, such as crostin, crocin, safranal, and picrocrocin (Heydarian *et al*., 2022). Proposed antioxidant and anti-inflammatory mechanisms of this compound include increased glutathione, antioxidant enzymes, and erythroid-related factor 2 (Nrf2) activity as well as downregulation of iNOS, NFκB expression, and downregulation of inflammatory cytokines. A mouse colitis model has shown that crocin can prevent colitis-associated carcinogenesis by improving wound healing and inflammation in chemically induced colitis (Ashktorab *et al*., 2019).

Zingiber officinale:

Zingiber officinale, or ginger, has been popular in herbal medicine for centuries and is used in Ayurveda, TCM, and TPM for a variety of conditions. The therapeutic effect of ginger is

attributed to bioactive terpenes and phenolic compounds such as gingerol, zingiberine and shogaol (Nikkhah-Bodaghi *et al.*, 2019). In mouse colitis models and laboratory studies, zinc's anti-inflammatory and antioxidant effects have been linked to the inhibition of NF-κB, enhanced production of pro-inflammatory cytokines, reduced synthesis of pro-inflammatory cytokines, and increased levels of superoxide dismutase (SOD) and glutathione. Additionally, cloves have showed antibacterial and anticancer properties and may influence the gut microbiome by promoting the growth of bacteria that produce short-chain fatty acids (SCFAs), which are thought to possess anti-inflammatory effects (Mao *et al.*, 2019). Wang *et al.* (2020) studied 2,000 mg of ginger capsule powder daily in two divided doses with placebo in 64 patients with moderate ulcerative colitis. At week 12 the mean SCCAI score in the ginger group showed a significantly greater reduction in the mean SCCAI score compared to the placebo group. Although there was no difference in TAC, malondialdehyde (MDA) levels were significantly reduced zinc group, levels were significantly lower compared to the placebo group at the 12 weeks (Nikkhah-Bodaghi *et al.*, 2019).

Conclusion

Ulcerative colitis (UC) is a typical kind of inflammatory bowel disease. Because of the inadequately perceived pathogenesis, safe and effective restorative procedures are as yet deficient. A few natural products, for example, flavonoids are drawing in more consideration as new specialists for helpful use. Flavonoids are the most plentiful regular cancer prevention agents tracked down in plants and human food sources. Naringenin is a flavonoid tracked down in oranges, tomatoes, cherries and cocoa. Naringenin is broadly utilized as a therapeutic plant to treat specific sicknesses. It has likewise been displayed to have a few cell reinforcement and calming potential.

Naringenin lessens the impact of dextran sodium sulfate on digestive edema in rodents. NG has been displayed to have some cell reinforcement, antitumor, and mitigating pharmacological possibilities in testing since naringenin has the property to create sufficient hydroxyl (- Goodness) replacements that permit rummaging of ROS. In this manner, as in IBD, it can decrease and/or improve neurotic circumstances in which oxidation or aggravation is remembered to assume a significant part. Given the widespread use of herbal supplements in the United States, it is imperative that healthcare providers become educated on how to guide their patients in the safe use of herbal medicines.

Ethical Statement

This is a review article hence no Ethical Approval required.

Author Contributions

Each author has contributed equally to the study's planning, analysis, writing, and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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