

Integrative Approaches to Ulcerative Colitis

Possible Solutions to Treatment Options

Rahm, Christina, M.S., Ed.D., Ph.D.

January 10, 2024

Ulcerative colitis (UC)

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that causes inflammation and ulcers in the lining of colon and rectum. It is an autoimmune condition where the immune system attacks the tissues of the colon, leading to inflammation and damage (Kevans et al., 2020). UC often begins between ages 15-30 but can occur at any age. The exact causes are unknown, but genetic and environmental factors likely play a role. The main symptoms of UC include recurring diarrhea containing blood, mucus, or pus; abdominal pain; frequent bowel movements; fatigue; appetite/weight loss. Symptom severity varies and depends on the extent of inflammation. Some experience mild symptoms or long remission periods mixed with flare-ups where symptoms worsen (Kevans et al., 2020). Extra-intestinal manifestations like painful joints, eye irritation, and skin conditions may also occur. Triggers for flare-ups are not always clear but may include infections and stress. Prompt medical care is vital, especially for severe flares requiring hospitalization.

Ulcerative colitis (UC) is more prevalent among individuals of European descent and the African American population compared to other ethnicities. Its occurrence is relatively equal between men and women. Treatment focuses on relieving symptoms and maintaining remission. Mild-moderate flares can often be managed at home with medications like aminosalicylates, steroids, and immunosuppressants. More severe cases require hospitalization and intravenous medications. If treatments fail to control symptoms or the quality of life is significantly impacted, surgery to remove part or all of the colon may be necessary (Segal et al., 2021). This can involve diverting the small intestine to an abdominal stoma (ileostomy) or creating an internal ileoanal pouch.

Certain natural remedies and conventional drugs can complement prescribed medications, enhancing their effectiveness in managing ulcerative colitis (UC). Turmeric, rich in curcumin, serves as a powerful anti-inflammatory agent that helps reduce colon inflammation. Peppermint oil, particularly in enteric-coated capsules, acts as both an antispasmodic and anti-inflammatory compound, which may help alleviate abdominal pain, cramping, and discomfort often associated with ulcerative colitis by relaxing the smooth muscles of the gastrointestinal tract. Probiotic supplements support gut health by replenishing beneficial bacteria, rebalancing the microbiome, and reducing levels of inflammation-causing microbes. Omega-3 fatty acids promote gut lining integrity and help combat inflammation. Additionally, deficiencies in vitamin D and zinc are common, and addressing these through supplementation can alleviate symptoms. Research continues to support the effectiveness of these integrative approaches—curcumin, peppermint oil, probiotics, and omega-3s—as valuable complements to conventional treatments through their anti-inflammatory and gut-soothing properties.

Literature Review

The inflammatory bowel disease ulcerative colitis (UC) is characterized by recurring and remitting inflammation of the colonic mucosa. It typically starts in the rectum and can extend proximally to involve the entire colon (Segal et al., 2021). The incidence and prevalence of UC are rising. The goals of UC treatment are to promptly resolve symptoms, heal inflamed mucosa, and improve patients' quality of life. The key to optimal management is engaging patients to monitor their symptoms and adhere to therapies so treatment can be escalated when necessary (Segal et al., 2021). First-line therapies for mild-moderate UC are 5-aminosalicylate acid (5-ASA) medications. UC patients with clinically and endoscopically quiescent disease histological markers of inflammation are related to increased danger of subsequent disease

relapse. Even in mucosal healing, active microscopic inflammation was observed in 33% of patients (Kevans et al., 2020). Certain key histological features are associated with a shorter time to relapse. Basal plasmacytosis (BPC) and active histological inflammation predict earlier relapse. The presence of BPC nearly doubled the likelihood of relapse at 18 months. Meanwhile, a Geboes score (GS) consistent with active inflammation more than tripled the risk (Kevans et al., 2020). This underscores the point that persistent histological inflammation, despite mucosal healing, portends a clinically significant risk of symptomatic relapse.

Relapsing patients tend to need more aggressive medical therapy over time. BPC and active microscopic inflammation are linked to a shorter time to corticosteroid exposure. This likely reflects treatment escalation in high-risk patients with smoldering or recurrent disease activity. There is no association with biologics or surgery, but this may relate to the tertiary care setting and prescribing patterns (Kevans et al., 2020). Ultimately, UC patients with mucosal healing but residual microscopic inflammation demonstrate a tendency towards earlier symptomatic relapse, necessitating more intensive medical treatment. The key histological features predicting relapse risk include BPC and GS-defined active inflammation. These findings indicate mucosal healing alone may not be sufficient. Achieving both endoscopic and histological remission could be the optimal therapeutic target (Segal et al., 2021). Clinical decisions should take into account both endoscopic and microscopic disease activity to anticipate and hopefully mitigate the risk of relapse in UC patients.

Among the most known symptoms of ulcerative colitis include abdominal pain, usually crampy, an urgent need to defecate, and diarrhea with bloody, and mucous stools. The diarrhea is typically frequent, with up to 10 or more daily bowel movements during acute flares. Other gastrointestinal symptoms may include fatigue, malaise, loss of appetite, and weight loss

(Mamootil, 2023). During acute exacerbations, patients often describe feeling extremely ill. The abdominal pain is usually abrupt in nature and associated with extreme urgency to defecate (Peppercorn & Kane, 2020). The stools contain blood, mucous, and pus. Severe rectal pain and bleeding are also common. Fulminant colitis may lead to more than ten stools per day, continuous bleeding, abdominal distension, fever, and anorexia. Extra-intestinal manifestations may include joint pain, eye inflammation, rashes, and liver abnormalities. During periods of disease remission, patients may experience mild and nonspecific symptoms like fatigue, weakness, bloating, and abdominal discomfort without overt diarrhea or bleeding (Peppercorn & Kane, 2020). The course of ulcerative colitis is marked by periods of exacerbation and remission.

Symptoms of UC range from mild discomfort to severe pain. The urgency to have a bowel movement can be sudden and intense, sometimes leading to fecal incontinence or inability to hold in stool until reaching a bathroom. Other common gastrointestinal symptoms are loss of appetite, nausea, vomiting, and weight loss. In addition to the digestive issues caused directly by the inflammation of the bowel, UC can lead to various extraintestinal manifestations (Seyedian et al., 2019). These symptoms extend beyond the intestines, involving inflammation and discomfort in various organs, including the eyes, mouth, skin, joints, kidneys, and liver. Common extraintestinal manifestations include eye redness or pain, mouth ulcers, skin conditions like erythema nodosum, swollen and painful joints, painful urination caused by kidney inflammation, and primary sclerosing cholangitis, which affects the liver's bile ducts (Jangra, 2019). Anemia due to blood loss in stool is also frequently observed.

The signs and symptoms of UC tend to flare up and subside over time. Mild to moderate symptom flares alternate with periods of remission when symptoms disappear. The severity of symptoms often correlates with how much of the colon is inflamed. Those with inflammation

limited to the rectum (proctitis) typically have milder symptoms than those with more extensive inflammation higher up in the colon (Seyedian et al., 2019). However, even mild intermittent symptoms can negatively impact quality of life. Symptoms usually continue recurring periodically throughout the person's lifetime after initial diagnosis.

The lack of clinical symptoms characterizes the remission period in UC, but persistent underlying inflammation often remains. Achieving mucosal healing (MH) on endoscopy has become an essential target during remission, as MH is associated with lower rates of relapse, hospitalization, surgery, and UC-associated colorectal cancer (Kanazawa et al., 2019). However, even in patients who achieve MH, relapse still occurs in a proportion of patients. Thus, the presence of residual microscopic inflammation is not detectable on endoscopy. The importance of targeting histological healing and clinical and endoscopic remission is now recognized to improve further UC outcomes (Kevans et al., 2020). However, no studies have directly compared the degree of histological inflammation with endoscopic findings in patients who remain in sustained remission for long periods. It would be informative to assess histological inflammation, specifically in UC patients with prolonged endoscopic remission. This could help determine if the degree of histological healing correlates with the risk of relapse even once MH is achieved.

The goal of treatment for Ulcerative Colitis (UC) is to achieve clinical remission (resolution of rectal bleeding and diarrhea) and endoscopic remission (normal endoscopy findings). Treatment options depend on disease severity and location. Mild-moderate UC is treated first-line with oral and rectal mesalamine formulations, with the addition of corticosteroids if unresponsive (Park & Cheon, 2022). Moderate-severe UC is treated with medications like infliximab, adalimumab, golimumab, vedolizumab, ustekinumab, or oral medication tofacitinib. These treatments target inflammatory pathways to reduce inflammation.

Combination therapy with a biologic plus an immunomodulator like azathioprine can be more effective than monotherapy (Kayal & Shah, 2019). Acute severe UC requires hospitalization with intravenous steroids, then escalation to infliximab or cyclosporine if unresponsive to reduce the risk of colectomy. For patients with inadequate response to 5-ASAs, treatment is escalated to immunosuppressants or biologics, with choice dependent on several factors. Despite medical therapy, some patients still require surgery, including restorative procedures like ileal pouch-anal anastomosis or permanent ileostomy (Segal et al., 2021). The choice of therapy depends on disease severity, location, and patient factors to achieve clinical and endoscopic remission to minimize complications over time.

Sulfasalazine (SSZ) is an anti-inflammatory and immunosuppressive drug used for decades in treating ulcerative colitis. The key active ingredient in sulfasalazine is 5-aminosalicylic acid (5-ASA), which can directly act on inflamed intestinal mucosa. Sulfasalazine effectively reduces symptoms and improves outcomes in ulcerative colitis patients (Zhang et al., 2022). Sulfasalazine has antibacterial properties that help normalize gut flora, which is often dysregulated in UC. Its immunosuppressive effects also help reduce autoimmune attacks on the colon. Sulfasalazine (SSZ) works locally in the gut, where bacterial azoreductases in the colon break the azo bond between sulfapyridine and 5-aminosalicylate. This process releases 5-aminosalicylate, the active component responsible for its therapeutic effects (Asgharzadeh et al., 2021).

This active metabolite then works to reduce a variety of inflammatory mediators that propagate inflammation in colitis, including tumor necrosis factor α , interleukin 1β , interleukin 6, and nuclear factor κB signaling.

The antioxidant effects of 5-aminosalicylate also help attenuate oxidative stress in the inflamed colonic mucosa. Additionally, sulfapyridine gets absorbed systemically to inhibit T-cell proliferation and modulate cytokine production. The additive beneficial effects of SSZ and valsartan point to the potential for SSZ combination therapy approaches in ulcerative colitis treatment (Zhang et al., 2022). Overall, this preclinical study reinforces SSZ as an effective therapy for reducing gastrointestinal inflammation in colitis models through decreasing inflammatory cytokines, preserving mucosal integrity, alleviating oxidative stress, and working synergistically with other agents like valsartan. However, some patients discontinue sulfasalazine due to side effects like nausea, headache, and rash. It also interferes with folate absorption, so supplementation is often needed. Sulfasalazine is most effective for mildly to moderately active UC rather than severe disease.

Koyama et al. (2022) study used a silicon (Si)-based agent that generated hydrogen gas when ingested and reacted with water in the gastrointestinal tract. The hydrogen gas likely acted as an antioxidant, reducing oxidative stress and contributing to UC. The Si-based agent alleviated symptoms, inflammation, and oxidation in a mouse model of UC. Silica, a source of silicon, may produce hydrogen gas in the body through a similar mechanism when ingested. Supplementing with silica has the potential to help reduce oxidative stress and inflammation associated with ulcerative colitis (Koyama et al., 2022). However, more research should be done to determine if silica can generate significant and sustained amounts of hydrogen gas in the gastrointestinal tract, like the Si-agent used in the study. Trace minerals like selenium, zinc, and manganese serve as cofactors for antioxidant enzymes in the body, like glutathione peroxidase and superoxide dismutase. UC patients are often deficient in antioxidants and trace elements. Zinc, selenium, copper and manganese are all trace elements which maintain the integrity of

intestinal mucosal barrier. Supplementing with a balanced blend of trace elements could potentially boost endogenous antioxidant enzyme activity and help mitigate oxidative damage associated with UC (Haghighatdoost et al., 2023). Moreover, Vitamin C is a potent antioxidant that could help counteract oxidative stress implicated in UC. Quercetin and Vitamin K2 play a crucial role in managing inflammation by inhibiting inflammatory pathways, reducing oxidative stress, and improving intestinal barrier function. They also support wound healing and help regulate the gut microbiota, contributing to overall gut health. Some research indicates that UC patients' vitamin C levels are lower than healthy individuals. Supplementing with vitamin C may help restore antioxidant capacity and reduce inflammation (Jarmakiewicz-Czaja, 2023). However, high doses of vitamin C can cause gastrointestinal side effects, so tolerated doses would need to be determined.

Several natural compounds demonstrate promise as safer therapeutic options for UC. N-acetyl L-tyrosine, a modified amino acid, has antioxidant and anti-inflammatory properties that may aid UC treatment. Anhydrous caffeine and L-theanine found in green tea exhibit immunosuppressive effects that could reduce inflammatory flares in UC (Chen et al., 2023). Pine bark extract contains proanthocyanidins with potent antioxidant capacities that may help resolve oxidative stress underlying UC pathogenesis. Curcumin, the main bioactive molecule in turmeric, has well-established anti-inflammatory and immunomodulating activities relevant to UC therapy. Velvet bean seed contains L-dopa which has anti-inflammatory properties that can help soothe intestinal inflammation associated with ulcerative colitis. Pine bark contains proanthocyanidins and polyphenols which also have anti-inflammatory effects and can help reduce swelling and irritation in the colon (Gupta et al., 2022). Vitamin D also modulates immune responses, and deficiencies are prevalent in IBD patients.

Black cumin seed oil, derived from *Nigella sativa* seeds, holds a rich composition of antioxidants, particularly thymoquinone, which inhibited inflammation and supported healing in rodent colitis models. Resveratrol from grape skins potently inhibits inflammatory mediators and demonstrates efficacy in murine UC models. Raspberry ketones prevented colonic injury in chemically-induced UC rodent models, attributed to suppression of inflammatory signaling pathways (Chen et al., 2023). Apple cider vinegar contains probiotics and polyphenols that can balance gut microbiota and restrain colitis in animal models. Aloe vera gel has an array of bioactive polysaccharides and anthraquinones, which protect against experimental colitis through broad anti-inflammatory and wound-healing properties. Moreover, capsaicin, an ingredient in cayenne pepper, has anti-inflammatory qualities that may lessen intestinal inflammation linked to ulcerative colitis. Pomegranate seed powder and blueberries can lessen intestinal tissue damage and inflammation as they contain antioxidants and polyphenols. MCT coconut oil offers antibacterial and anti-inflammatory properties in addition to providing readily absorbed nutrients to support intestinal repair.

Ulcerative Colitis (UC) patients have widespread DNA hypomethylation in various cell types like the “intestinal epithelial cells and immune cells” (Marangoni et al., 2023). Diet can influence epigenetic processes and modulate ulcerative colitis (UC) inflammation. Nutrients like folate, vitamin B12, methionine, choline, and betaine act as methyl donors that contribute to DNA and histone methylation, altering gene expression profiles related to intestinal inflammation. Patients with ulcerative colitis (UC) often experience a deficiency in key methyl donors. Supplementation, as suggested by Marangoni et al. (2023), may help restore balanced methylation patterns and normalize the expression of genes critical for immune regulation and intestinal barrier function. By aiding in the metabolism of nutrients like methionine and folate

and enzymatic processes, vitamins B2, B6, and B12 also indirectly assist methylation. Thus, maintaining proper methylation and gene expression may be facilitated by eating a balanced diet that includes sufficient amounts of these micronutrients. Furthermore, the modulation of epigenetic markers by vitamins A and D influences inflammatory responses. The enzymes methyltransferase and acetyltransferase, which regulate methylation and acetylation, are bound to intestinal cell receptors by vitamin D (Chen et al., 2023). Through alteration of these histone modifications, vitamin D alters the expression of immunogenes. Some researchers propose that maintaining adequate vitamin D levels may help reduce inflammation in patients with ulcerative colitis (UC). Vitamin D3 modulates and strengthens the immune system which helps bring the body's inflammatory response under control. Anti-inflammatory gene expression is up regulated through supplementation (Marangoni et al., 2023). Vitamin A plays a key role in supporting immune balance by promoting the generation of regulatory T cells in the intestinal lining, enhancing immune tolerance. Consuming sufficient amounts of vitamin A through dietary sources like fish, eggs, liver, and fortified milk may help reduce the severity of UC flare-ups.

However, uncertainties remain regarding optimal intakes of specific nutrients for epigenetic impact and differences between dietary sources and supplements. High vitamin A doses could have unintended epigenetic consequences. Overall, nutritional status contributes to epigenetic dysregulation and inflammation in UC (Marangoni et al., 2023). A balanced diet ensuring sufficient intake of key methyl donors, B vitamins, A and D may help restore gene expression patterns and restrain inflammation. However, personalized nutrient requirements and sources need further elucidation to effectively translate diet into epigenetic-based UC therapies. Monitoring patients' nutritional status and tailoring diet interventions to their deficits shows promise for managing this chronic disease.

Fiber helps nourish the good bacteria in the gut microbiome. Inulin, green banana flour, apple fiber, wheat grass, barley grass, alfalfa leaf, flax seed, and psyllium husk are all sources of dietary fiber and prebiotics. The extra fiber and prebiotics from these nutrients can aid in reestablishing the proper balance of the gut flora, which is frequently upset in those suffering from ulcerative colitis (Seyedian et al., 2019). A probiotic, or helpful strain of bacteria, *Bacillus coagulans* can help increase the number of healthy bacteria in the gut. Antioxidants and minerals in spirulina and wheatgrass aid in reducing intestinal inflammation and accelerating the recovery of the damaged colon tissue linked to ulcerative colitis. Omega-3 fatty acids that reduce inflammation are also found in flaxseeds. By balancing the gut flora, lowering inflammation in the colon, and promoting healthy intestinal healing and function, these all-natural substances can help reduce ulcerative colitis flare ups and symptoms (Beane et al., 2021). Green leafy vegetables and algae are packed with vitamins, minerals, and antioxidants that can help reduce intestinal inflammation. Additionally, chlorophyll, abundantly found in chlorella, may support the healing process of the intestinal lining. The high levels of fiber, vitamin C, vitamin K, and sulforaphane found in broccoli, kale, spinach, cabbage, and parsley help to control immunological responses in the intestines. The abundant nutritional profiles lessen ulcerative colitis symptoms by fostering stomach tissue regeneration, protecting the intestinal lining, and promoting good intestinal bacteria. Over time, eating these greens can aid in managing the condition.

NAD-centered therapies can manage inflammatory bowel disease (IBD), ulcerative colitis (UC), and Crohn's disease. Nicotinamide adenine dinucleotide (NAD) coenzyme is found in all living cells involved various cellular processes like energy metabolism, mitochondrial function, aging, and immune responses. NAD exists in two primary forms: oxidized NAD⁺ and

reduced NADH (Tang et al., 2022). Maintaining optimal NAD levels is essential for proper cellular function and survival. There is growing interest in investigating the therapeutic potential of NAD supplementation or the modulation of its biosynthesis for managing various diseases.

In UC, chronic inflammation of colon leads to symptoms like abdominal pain, diarrhea, rectal bleeding, and weight loss. Studies have found that intestinal NAD levels are decreased in IBD patients and experimental colitis models (Segal et al., 2021). This NAD depletion seems to promote inflammation and disrupt intestinal barrier integrity. Restoring NAD levels helped mitigate colitis severity by reducing inflammatory cytokines, enhancing epithelial regeneration, and improving gut barrier function. Nicotinamide phosphoribosyltransferase (NAMPT), a critical enzyme in NAD biosynthesis, plays a pivotal role in regulating intestinal inflammation and facilitating tissue repair. Research by Tang et al. (2022) indicates that NAMPT overexpression increases NAD levels and alleviates experimental colitis, while its inhibition exacerbates the condition. NAMPT likely exerts anti-inflammatory effects by inhibiting NF- κ B signaling. Additionally, extracellular NAMPT can directly enhance epithelial cell migration and wound closure. Hence, modulating NAMPT/NAD is a promising approach for colitis treatment.

In addition to controlling inflammation, NAD plays a critical role in maintaining essential gut processes such as epithelial regeneration, antimicrobial peptide secretion, and mitochondrial function, all of which are disrupted in conditions like colitis and other inflammatory bowel diseases (IBD) (Tang et al., 2022). For example, NAD supplementation has been shown to enhance intestinal stem cell regeneration in colitis models. Supplementation with NAD precursors increased the production of Paneth cell defensins, which fortify the mucosal barrier against pathogens. Furthermore, replenishing NAD improved mitochondrial function and reduced oxidative stress, addressing key factors underlying IBD pathology.

Some medicines used in ulcerative colitis (UC) treatment include Corticosteroids. This induces remission of active, moderate-to-severe ulcerative colitis (UC), especially in cases of acute severe disease requiring hospitalization. Oral prednisone at 40-60 mg daily is usually the first-line corticosteroid treatment. If symptoms do not respond adequately to oral steroids within 3-5 days, intravenous methylprednisolone should be initiated at 40-60 mg daily while the patient is closely monitored in the hospital (Tripathi & Feuerstein, 2019). About two-thirds of patients will respond to intravenous corticosteroids. There are no set recommendations for steroid tapering, but a gradual taper is advised only after significant clinical improvement occurs. While highly effective for inducing remission, corticosteroids have no role in maintaining remission and are associated with many irreversible dose-related toxicities involving multiple organ systems. These include obesity, diabetes, hypertension, glaucoma, cataracts, avascular necrosis, insomnia, depression, and immunosuppression, leading to increased risks of opportunistic infections (Tripathi & Feuerstein, 2019). Such infections are even more likely when steroids are combined with other immunosuppressive UC therapies.

Due to the lack of efficacy in sustaining remission and their unfavorable side effect profile, steroids should never be used for long-term UC therapy. Instead, they serve as a short-term "bridge" to induce remission, which can be maintained using steroid-sparing therapies such as thiopurines, anti-TNF biologics, anti-integrins, or JAK inhibitors. About 15% of UC patients fail to respond adequately to intravenous corticosteroids and are considered to have steroid-refractory disease (Tripathi & Feuerstein, 2019). In such cases, second-line intravenous treatment with infliximab or cyclosporine should be promptly initiated.

The 5-aminosalicylate (5-ASA) class of medications, including sulfasalazine, mesalamine, and diazo-bonded 5-ASA, is widely recognized as the first-line treatment for

mild-to-moderate ulcerative colitis (UC). Sulfasalazine, the earliest 5-ASA drug, has seen reduced use due to side effects from its sulfapyridine component, leading to increased reliance on mesalamine and diazo-bonded 5-ASA for their improved safety profiles (Park & Cheon, 2022). These formulations use various delivery methods to target inflamed areas of the colon effectively. Combined oral and topical 5-ASA therapy is often recommended for extensive mild-to-moderate UC to maximize drug concentrations in the colonic mucosa. The European Crohn's and Colitis Organisation and the American Gastroenterological Association recommend 5-ASA compounds for over 90% of UC patients shortly after diagnosis.

5-aminosalicylate (5-ASA) offers a range of therapeutic regimens and delivery models, enabling patients and physicians to collaborate in selecting a treatment plan tailored to the patient's preferences, disease characteristics, and adherence capabilities. However, poor compliance remains a significant challenge due to factors such as high pill burden, frequent dosing, side effects, and forgetfulness (Tripathi et al., 2021). Simplified dosing schemes and educational programs can help address these barriers and enhance adherence. Despite these challenges, 5-ASA remains a safe and effective first-line treatment for mild-to-moderate UC, with various formulations allowing for personalized care and improved outcomes. Continued efforts are needed to support patients in overcoming adherence obstacles and fully realizing the benefits of 5-ASA therapy.

Conclusion

Ulcerative colitis (UC), a form of inflammatory bowel disease, has a profound impact on quality of life. While its exact pathophysiology remains unclear, it is believed to result from a complex interplay of genetic predisposition, environmental influences, gut microbiota imbalances, and an abnormal immune response. Mild-moderate UC can often be managed with

5-aminosalicylate formulations (5-ASA's) like sulfasalazine and mesalamine. Though adherence is suboptimal, these compounds act locally on inflamed mucosa through anti-inflammatory and antioxidant mechanisms. For non-responsive mild-moderate cases or moderate-severe flares at onset, corticosteroids effectively bridge to remission induction, which can then be maintained with steroid-sparing immunosuppressants. Anti-TNF therapies have revolutionized UC treatment, providing durable remission through selective immune pathway inhibition for many patients. Agents targeting other cytokines and integrins expand options for precision therapy. Despite optimal medical management, a subset of patients still require colectomy. Ileal pouch-anal anastomosis enables gastrointestinal continuity but risks pouchitis. Some patients undergo permanent ileostomy. Adjunctive therapies like curcumin, probiotics, and zinc supplementation demonstrate potential through anti-inflammatory, antioxidant, and gut barrier-promoting mechanisms. Still, more research is needed regarding their clinical translation.

Overall, current ulcerative colitis (UC) treatment employs a multi-tiered approach, utilizing aminosalicylates for mild cases, corticosteroids for managing flare-ups, and immunosuppressants for long-term maintenance. Biologic therapies offer targeted immune modulation, while surgery is reserved for cases where medical treatments prove ineffective. Effective treatment plans must also account for individual patient preferences, risks, lifestyle considerations, cost, and accessibility. While achieving mucosal healing remains a critical goal, microscopic inflammation may persist undetected. As advancements in immunopathogenesis and nutrigenomics deepen our understanding of UC, future therapies hold the promise of more precise and potentially curative options driven by these mechanistic insights.

References

- Asgharzadeh, F., Yaghoubi, A., Nazari, S. E., Hashemzadeh, A., Hasanian, S. M., Avan, A., Javandoost, A., Ferns, G. A., Soleimanpour, S., & Khazaei, M. (2021). The beneficial effect of combination therapy with sulfasalazine and valsartan in the treatment of ulcerative colitis. *EXCLI journal*, 20, 236–247. <https://doi.org/10.17179/excli2021-3370>
- Beane, K. E., Redding, M. C., Wang, X., Pan, J. H., Le, B., Cicalo, C., ... & Kim, J. K. (2021). Effects of dietary fibers, micronutrients, and phytonutrients on gut microbiome: a review. *Applied Biological Chemistry*, 64(1), 1-18.
- Chen, J., Ruan, X., Yuan, S., Deng, M., Zhang, H., Sun, J., Yu, L., Satsangi, J., Larsson, S. C., Therdoratou, E., Wang, X., & Li, X. (2023). Antioxidants, minerals and vitamins in relation to Crohn's disease and ulcerative colitis: A Mendelian randomization study. *Alimentary pharmacology & therapeutics*, 57(4), 399–408. <https://doi.org/10.1111/apt.17392>
- Gupta, M., Mishra, V., Gulati, M., Kapoor, B., Kaur, A., Gupta, R., & Tambuwala, M. M. (2022). Natural compounds as safe therapeutic options for ulcerative colitis. *Inflammopharmacology*, 30(2), 397–434. <https://doi.org/10.1007/s10787-022-00931-1>
- Haghighatdoost, F., Mohammadifard, N., & Sarrafzadegan, N. (2023). Trace Minerals 31. *Handbook of Food Bioactive Ingredients*, 1021.
- Jangra, J. (2019). Brief Review on Ulcerative Colitis and Associated Disorders. *J Gastrointest Dig Syst*, 9(588), 2.
- Jarmakiewicz-Czaja, S., Ferenc, K., & Filip, R. (2023). Antioxidants as Protection against Reactive Oxidative Stress in Inflammatory Bowel Disease. *Metabolites*, 13(4), 573. <https://doi.org/10.3390/metabo13040573>

- Kanazawa, M., Takahashi, F., Tominaga, K., Abe, K., Izawa, N., Fukushi, K., Nagashima, K., Kanamori, A., Takenaka, K., Sugaya, T., Iijima, M., Takada, A., Imai, Y., Hiraishi, H., & Irisawa, A. (2019). Relationship between endoscopic mucosal healing and histologic inflammation during remission maintenance phase in ulcerative colitis: a retrospective study. *Endoscopy international open*, 7(4), E568–E575.
<https://doi.org/10.1055/a-0869-7619>
- Kayal, M., & Shah, S. (2019). Ulcerative Colitis: Current and Emerging Treatment Strategies. *Journal of clinical medicine*, 9(1), 94. <https://doi.org/10.3390/jcm9010094>
- Kevans, D., Kirsch, R., Dargavel, C., Kabakchiev, B., Riddell, R., & Silverberg, M. S. (2020). Histological Markers of Clinical Relapse in Endoscopically Quiescent Ulcerative Colitis. *Inflammatory bowel diseases*, 26(11), 1722–1729. <https://doi.org/10.1093/ibd/izz308>
- Koyama, Y., Kobayashi, Y., Hirota, I., Sun, Y., Ohtsu, I., Imai, H., ... & Shimada, S. (2022). A new therapy against ulcerative colitis via the intestine and brain using the Si-based agent. *Scientific Reports*, 12(1), 9634.
- Mamootil D. (2023). Pediatric Ulcerative Colitis in Siblings. *Cureus*, 15(6), e40829.
<https://doi.org/10.7759/cureus.40829>
- Marangoni, K., Dorneles, G., da Silva, D. M., Pinto, L. P., Rossoni, C., & Fernandes, S. A. (2023). Diet as an epigenetic factor in inflammatory bowel disease. *World journal of gastroenterology*, 29(41), 5618–5629. <https://doi.org/10.3748/wjg.v29.i41.5618>
- Park, J., & Cheon, J. H. (2022). Updates on conventional therapies for inflammatory bowel diseases: 5-aminosalicylates, corticosteroids, immunomodulators, and anti-TNF- α . *The Korean journal of internal medicine*, 37(5), 895–905.
<https://doi.org/10.3904/kjim.2022.132>

- Peppercorn, M. A., & Kane, S. V. (2020). Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults. *UpToDate* (Accessed on December 2014).
- Segal, J. P., LeBlanc, J. F., & Hart, A. L. (2021). Ulcerative colitis: an update. *Clinical medicine (London, England)*, 21(2), 135–139. <https://doi.org/10.7861/clinmed.2021-0080>
- Seyedian, S. S., Nokhostin, F., & Malamir, M. D. (2019). A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. *Journal of medicine and life*, 12(2), 113–122. <https://doi.org/10.25122/jml-2018-0075>
- Tang, Y., Liu, X., Feng, C., Zhou, Z., & Liu, S. (2022). Nicotinamide phosphoribosyltransferase (Nampt) of hybrid crucian carp protects intestinal barrier and enhances host immune defense against bacterial infection. *Developmental & Comparative Immunology*, 128, 104314.
- Tripathi, K., & Feuerstein, J. D. (2019). New developments in ulcerative colitis: latest evidence on management, treatment, and maintenance. *Drugs in context*, 8.
- Tripathi, K., Dong, J., Mishkin, B. F., & Feuerstein, J. D. (2021). Patient preference and adherence to aminosalicylates for the treatment of ulcerative colitis. *Clinical and Experimental Gastroenterology*, 343-351.
- Zhang, H., Li, Y., Xue, Y., & Zhou, C. (2022). Systematic review of adjuvant sulfasalazine in the treatment of ulcerative colitis. *MEDS Clinical Medicine*, 3(2), 100-104.