Exploring herbal and current medicines: A comprehensive review on integrative approaches for ulcerative colitis

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***Abstract*- Ulcerative colitis (UC) is a chronic and recurring gastrointestinal disease with a rising global incidence, impacting individuals' quality of life. This comprehensive review explores the causes, prevalence, pathophysiology, and various treatment options for UC, emphasizing the need for personalized therapeutic approaches. The intricate signaling pathways, including NF-κB, JAK-STAT, MAPK, Wnt/β-Catenin, TLR-MyD88, and PI3K-Akt-mTOR, play crucial roles in UC pathogenesis, providing targets for novel therapies. The diagnosis involves clinical history, stool tests, colonoscopy, and imaging, while treatment includes medications, surgery, and emerging therapies. Herbal and Chinese medicines are gaining attention, with current research highlighting their bioactivity and clinical efficacy. However, challenges such as lack of standardization and safety concerns must be considered. Managing UC involves a holistic approach, integrating medication, dietary changes, and surgical interventions, recognizing the impact on patients' quality of life. Ongoing research aims to unravel UC complexities, paving the way for personalized and targeted therapies to address the evolving landscape of this challenging condition. The article underscores the importance of addressing economic burdens, optimizing resource allocation, and fostering continuous research to improve treatment options and patient outcomes.**

***Index Terms*: Chinese medicines, herbal medicines, ulcerative colitis, management of ulcerative colitis.**

I.INTRODUCTION

Ulcerative colitis is a chronic and relapsing gastrointestinal disease, which is characterized by inflammatory responses in the colon's mucosa, affecting the distal colon and rectum, usually with periods of remission and relapse [1]. It is a challenging condition that can significantly impact the quality of life for those affected. With no known definitive cure, effective management and treatment are crucial for improving symptoms and preventing complications [2]. Despite being extensively studied, the exact causes remain unclear, but it is known that various factors including the environment, immune system, gut microbiome, and genetic predisposition play vital roles in the etiology of ulcerative colitis [3]. This disease presents with significant clinical symptoms such as bloody diarrhea, abdominal pain, fatigue, urgency, and fecal incontinence [4]. It is essential to note that the Montreal classification categorizes the conditions based on their disease extent, which is crucial in predicting the severity and assessing management strategies [5]. Understanding the intricate signaling pathways in ulcerative colitis provides a foundation for developing targeted therapies [6]. Modulating the pathways holds the potential to interrupt the inflammatory cascade, promote mucosal healing, and provide novel treatment avenues for individuals with UC [7]. However, the heterogeneity of the signaling cascades among patients underscores the need for personalized therapeutic approaches in the management of ulcerative colitis [8]. Ongoing research in this field aims to unravel the complexities of these pathways, paving the way for more effective and tailored treatment strategies [9].

The impact on the quality of life for individuals living with ulcerative colitis is substantial, as the symptoms can be debilitating and significantly disrupt daily life. Furthermore, the lack of a definitive cure adds to the complexity of managing this chronic condition [10]. Patients often experience a fluctuating disease course, making it challenging to predict symptom severity and response to treatment [11]. The enduring absence of an absolute cure underscores the importance of enhancing current treatment modalities, emphasizing the significance of personalized care, and promoting ongoing research to advance the management of this condition [12]. In this comprehensive review, we will explore the causes, prevalence, pathophysiology, and various treatment options for ulcerative colitis, providing valuable insights for both patients and healthcare professionals. By gaining a deeper understanding of this condition, individuals can make informed decisions about their care and well-being.

II.EPIDEMIOLOGY

UC demonstrates steadily rising incidence and prevalence rates over recent decades, now recognized as a global disease with substantial clinical and economic implications [13]. Recent studies estimate approximately 1.6 million UC cases in the United States and over 2.2 million cases in Europe, indicating significant disease burden in industrialized nations [14]. Furthermore, peak incidence follows a bimodal age distribution, occurring between ages 15-30 years and a second spike from 50-70 years [15]. The factors provoking shifting epidemiological patterns remain ambiguous but may relate to westernization influences on environmental exposures and intestinal microbiota [16]. Clarifying epidemiological trends is imperative for healthcare infrastructure planning and resource mobilization [17].

III.AETIOLOGY AND PATHOPHYSIOLOGY

The pathogenesis of ulcerative colitis (UC) is multifactorial, involving intricate interactions between genetic, environmental, immunologic, and microbial factors [18]. Genetic predisposition, highlighted by heredity and specific variants such as those in the HLA system, plays a significant role, with individuals having a family history of IBD facing an elevated risk [19]. Immune dysregulation manifests as an inappropriate response in the gastrointestinal tract, with CD4+ T cells activation and the release of pro-inflammatory cytokines driving chronic inflammation [20]. Environmental factors, including microbiota dysbiosis and the hygiene hypothesis, contribute to an inflammatory milieu. Epithelial barrier dysfunction, characterized by impaired mucosal integrity and loss of tolerance to commensals, amplifies the interaction between luminal antigens and the immune system [21]. Vascular changes, such as angiogenesis and altered microvascular permeability, perpetuate inflammation. Environmental triggers like dietary factors and smoking, with its paradoxical effects, further impact UC development [22]. Autoimmunity, marked by the production of autoantibodies and an immune reaction in the colon, underscores the autoimmune aspect of UC [23]. Understanding these complexities is pivotal for tailoring therapeutic interventions, focusing on immune response modulation, mucosal barrier restoration, and microbial balance for more effective, personalized UC treatments [24]. Ongoing research continues to unravel UC's intricacies, offering insights into novel therapeutic avenues.

IV.SIGNALLING PATHWAYS IN UC

NF-κB Pathway:

The NF-κB pathway is a central regulator of the inflammatory response and is prominently implicated in the pathogenesis of ulcerative colitis (UC). Under normal conditions, NF-κB is sequestered in the cytoplasm by inhibitory proteins [25]. However, in UC, there is abnormal activation of NF-κB, leading to its translocation into the nucleus and subsequent upregulation of pro-inflammatory genes. This sustained activation contributes to the production of inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), perpetuating mucosal inflammation and tissue damage [26].

JAK-STAT Pathway:

The JAK-STAT pathway is essential for the regulation of immune responses. In UC, dysregulation of this pathway is observed, resulting in increased activation of Janus kinases (JAKs) and subsequent phosphorylation of Signal Transducer and Activator of Transcription (STAT) proteins [27]. The activated STAT proteins translocate to the nucleus and induce the expression of inflammatory genes. Targeting JAKs with specific inhibitors has shown promise in dampening the inflammatory response and has emerged as a therapeutic strategy for UC [28].

MAPK Pathway:

The MAPK pathway is crucial for transmitting signals from the cell surface to the nucleus, regulating cellular responses to extracellular stimuli. In UC, aberrant activation of the MAPK pathway contributes to the production of pro-inflammatory mediators and promotes apoptosis of intestinal epithelial cells [29]. This sustained activation plays a role in mucosal damage, perpetuating the inflammatory cascade in UC.

Wnt/β-Catenin Pathway:

The Wnt/β-Catenin pathway is vital for cell proliferation and differentiation. Dysregulation of this pathway in UC is associated with impaired tissue repair and regeneration [30]. Abnormal activation of Wnt signaling may contribute to the development of dysplasia and colorectal cancer in individuals with long-standing UC [31].

TLR-MyD88 Pathway:

The Toll-like receptor (TLR) pathway, particularly TLR-4, is involved in recognizing microbial components. In UC, increased activation of TLR-4 contributes to the inflammatory response [32]. Myeloid differentiation primary response 88 (MyD88) acts as a critical adapter molecule in this pathway, mediating the activation of downstream pro-inflammatory signaling cascades, further aggravating the inflammatory milieu in UC [33].

PI3K-Akt-mTOR Pathway:

The PI3K-Akt-mTOR pathway regulates cell growth and survival. Dysregulation of this pathway is observed in UC, contributing to increased inflammatory responses [34]. Additionally, impaired autophagy, a cellular process crucial for maintaining homeostasis, is associated with the aberrant activation of the PI3K-Akt-mTOR pathway in UC. This dysregulation influences the delicate balance between inflammation and tissue repair [35].

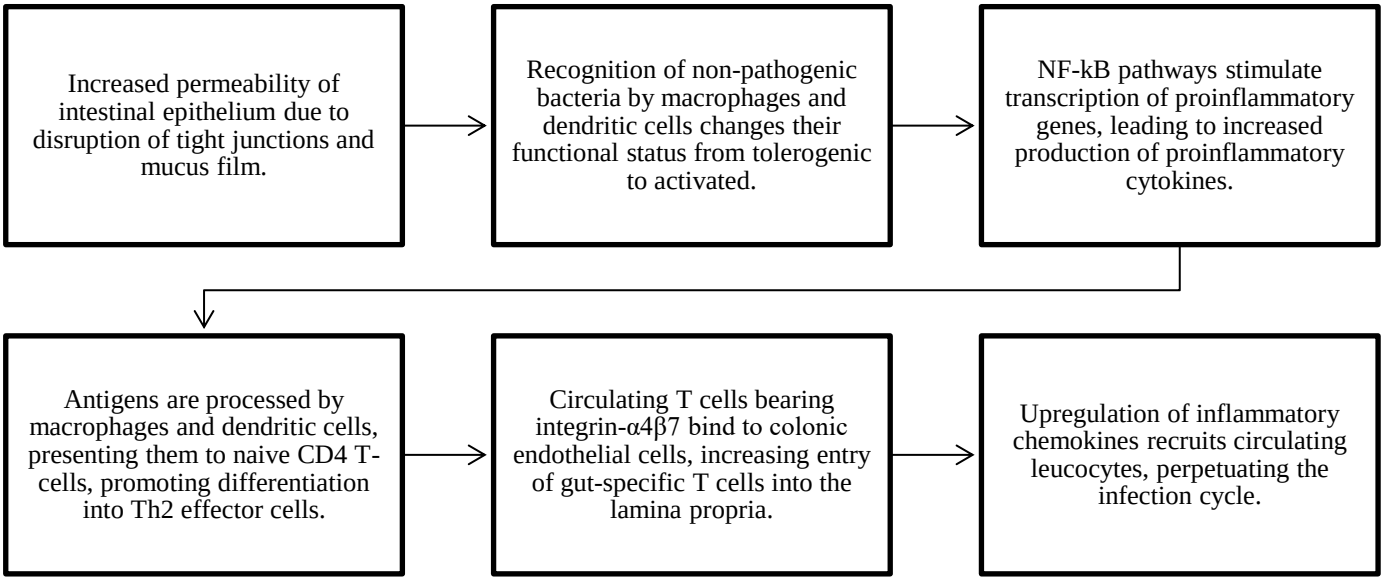

Fig.1 Pathogenesis of Ulcerative colitis

V.DIAGNOSIS AND ASSESSMENT

Diagnosing UC requires eliciting indicative clinical history, stool tests revealing infection or inflammation, colonoscopy with histopathology and potential cross-sectional imaging to exclude complications like structuring or perforation [36]. Follow-up ileocolonoscopic combined with validated endoscopic indexes like UCEIS and Mayo Scoring enable tracking mucosal recovery while guiding treatment decisions by stratifying disease severity [37]. Histological findings also predict prognosis by detecting precancerous cell changes warranting intervention. Therefore, diagnostic precision is imperative for timely and appropriate management.

VI.TREATMENT OF ULCERATIVE COLITIS

Ulcerative colitis (UC) is a chronic inflammatory disorder of the colon that often requires medical intervention for symptom control and disease management [38]. It's crucial to explore various treatment options to effectively manage the condition and improve the quality of life for individuals affected [39]. With the unpredictable nature of ulcerative colitis and its impact on daily functioning, the significance of a multifaceted approach to treatment cannot be overstated [40]. From medication and dietary adjustments to surgical interventions and emerging therapies, a comprehensive exploration of these options is essential for informed decision-making and personalized care.

Current medication treatments for ulcerative colitis typically include a range of options such as amino salicylates, corticosteroids, immunomodulators, and biologics [41]. These medications aim to reduce inflammation in the digestive tract and provide relief from symptoms [42]. Despite their effectiveness in managing flare-ups, these medications come with potential side effects, varying from mild to severe, and the consideration of long-term use is crucial. The impact of medication on the quality of life is an important aspect to carefully assess, encompassing elements such as adverse effects, treatment adherence, and the overall well-being of individuals living with ulcerative colitis [43].

Amino salicylates

One of the main pharmacological treatment classes utilized is the 5-aminosalicylic acid (5-ASA) compounds [44]. These compounds encompass a range of oral and topical agents with the primary goal of achieving remission through the decrease of inflammation (PMC) [45]. Their mechanism of action involves the inhibition of prostaglandin and leukotriene synthesis, ultimately leading to a reduction in the inflammatory response. In mild to moderate UC, 5-ASA compounds have been effective in inducing remission [46]. This class of drugs is particularly beneficial in treating proctosigmoiditis and left-sided colitis, with the potential to reduce the need for corticosteroids [47]. However, it is important to consider the potential side effects associated with 5-ASA compounds, such as nephrotoxicity and hepatotoxicity. Additionally, there are considerations such as drug interactions and adherence that need to be taken into account when prescribing these medications, especially for long-term use. These components are crucial when examining the role and effectiveness of 5-ASA compounds for treating ulcerative colitis [48].

Corticosteroids

Corticosteroids play a pivotal role in treating ulcerative colitis by effectively mitigating inflammation and alleviating symptoms [49]. They are indicated for use in moderate to severe cases of the condition, particularly when patients do

not respond to other forms of treatment. Additionally, corticosteroids can offer short-term benefits such as reducing intestinal inflammation and providing relief from symptoms like abdominal pain, diarrhea, and rectal bleeding [50]. However, there are long-term implications associated with their usage, including potential complications such as osteoporosis, hypertension, weight gain, and increased susceptibility to infections. These effects underscore the need for cautious consideration of the administration of corticosteroids in managing ulcerative colitis [51].

Immunosuppressants

Immunosuppressants play a significant role in managing moderate to severe cases of ulcerative colitis. In contrast to 5-aminosalicylic acid (5-ASA) compounds and corticosteroids, which work to induce remission in the disease, immunosuppressants are reserved for more severe and persistent cases [52]. Their effectiveness is comparable to other medications and they are generally reserved for patients who do not respond to common treatment modalities. Throughout the treatment process, close monitoring is essential to ensure patient safety and to manage the potential risks associated with these drugs. This involves regular blood tests and medical evaluations to check for side effects such as liver abnormalities, bone marrow suppression, [53] and an increased risk of infections, thus emphasizing the importance of monitoring for patient care [54].

Biologic Therapies

Biologic therapies represent a promising avenue for the treatment of ulcerative colitis, with several options currently available. Biologics, also known as biologic response modifiers, are genetically engineered proteins derived from living organisms [55]. These include tumor necrosis factor (TNF) inhibitors such as infliximab and adalimumab, which offer substantial benefits in inducing and maintaining remission in moderate to severe ulcerative colitis [56]. When selecting the appropriate biologic therapy, factors such as past reaction to specific medications, duration of effect, and the route of administration must be carefully considered to ensure the best outcomes for patients. Additionally, close monitoring for any adverse events and potential risks, including infections, infusion reactions, and long-term implications, is essential in the management of patients undergoing biologic therapy for ulcerative colitis [57].

Surgery

Surgical interventions for ulcerative colitis aim to provide relief for individuals who have not responded well to medication or who are experiencing severe complications [58]. These interventions include colectomy, proctocolectomy, and ileoanal pouch surgery. The success rates for these procedures are generally high, often leading to a significant improvement in symptoms and quality of life [59]. However, they do come with potential risks such as infection, pouch failure, and long-term complications. Patients need to carefully consider the impact of these risks alongside the potential benefits when choosing surgical options, taking into account their individual health circumstances and long-term goals [60].

Combination therapy for ulcerative colitis involves a comprehensive approach that combines medication, dietary changes, and surgical interventions. There is compelling evidence supporting the effectiveness of this integrated approach in managing the symptoms and progression of ulcerative colitis [61]. By adopting a holistic strategy, healthcare providers can address the multifaceted nature of this condition, taking into account not only the physical symptoms but also the emotional and social impact on patients' lives [62]. This approach acknowledges the interconnectedness of various treatment modalities and the potential synergistic effects that can result from their combination, offering a more comprehensive and personalized management strategy for individuals with ulcerative colitis [63].

When considering the effectiveness of ulcerative colitis treatment options, it is essential to analyze the success rates of different approaches [64]. The comparison between medication, dietary changes, and surgical interventions sheds light on their varying effectiveness. Alongside this, the consideration of individual patient response and the potential variability in treatment outcomes becomes crucial. It becomes evident that a personalized approach to treatment is imperative given the diverse responses and effectiveness levels of these interventions.

VII.MANAGING ULCERATIVE COLITIS: IMPACT ON QUALITY OF LIFE

Managing ulcerative colitis has a significant impact on the daily life and functioning of affected individuals. The physical, emotional, and social ramifications of treatment options must be carefully considered [65]. Each treatment approach can have varying effects on the overall quality of life, and it is crucial to compare these outcomes when determining the most suitable course of action for patients struggling with ulcerative colitis [66].

Dietary changes play a pivotal role in managing the symptoms of ulcerative colitis. The impact of diet on the severity and frequency of symptoms can be substantial, making it essential to understand and implement specific dietary recommendations [67]. Research indicates that a low-residue, low-fiber diet may help alleviate symptoms such as abdominal pain, diarrhea, and bloating [68]. Additionally, incorporating probiotics, omega-3 fatty acids, and avoiding trigger foods like spicy foods or dairy products could contribute to symptom relief [69]. Studies have shown promising outcomes in managing ulcerative colitis through dietary adjustments, highlighting the significant effectiveness of dietary changes as part of a holistic treatment approach.

VIII.SIDE EFFECTS AND COMPLICATIONS OF ULCERATIVE COLITIS TREATMENTS

An in-depth understanding of the potential side effects and complications associated with various treatment options for ulcerative colitis is crucial for informed decision-making [70]. Medication treatments, such as immunomodulators and biologics, may present risks such as increased susceptibility to infections, liver injury, and infusion reactions [71]. Surgical interventions, including colectomy and ileal pouch-anal anastomosis, carry the potential for complications such as pouchitis and bowel obstruction. Assessing the risks and benefits of these treatments allows for a comprehensive evaluation of their impact on the patient's well-being [72]. Moreover, discussing strategies to minimize and manage treatment-related adverse effects is essential in maximizing the safety and efficacy of the chosen therapeutic approach [73].

IX.EMERGING THERAPIES

The landscape of ulcerative colitis treatment is continually evolving, with new and promising therapies in development offering hope for improved outcomes [74]. These emerging therapies encompass a wide array of approaches, including novel medications, targeted biologic agents, and innovative surgical techniques [75]. The potential impact on the future of ulcerative colitis treatment is substantial, promising more effective symptom management, reduced disease progression, and improved quality of life for patients. However, the adoption of emerging therapies also brings forth challenges and opportunities, such as ensuring accessibility, managing potential risks, and addressing the associated economic implications. Exciting prospects lie ahead in leveraging these emerging treatment modalities to advance the care and well-being of individuals affected by ulcerative colitis [76].

X.HERBAL AND CHINESE MEDICINE TREATMENTS FOR ULCERATIVE COLITIS

The significance of incorporating herbal and Chinese medicines in the treatment of UC is substantial owing to their potential role in reducing inflammatory symptoms and promoting overall well-being [77]. With increasing interest in integrative and alternative medical treatments, understanding the effectiveness and implications for clinical practice is essential in delineating a promising trajectory for UC management [78]. Traditional Chinese Medicine (TCM) is rooted in principles that have been shaped over thousands of years. Fundamentally, TCM perceives health and illness as a balance in the body, with treatments tailored to achieve holistic equilibrium [79]. Throughout history, herbal medicines have been integral to treating Ulcerative Colitis [80]. Their roots trace back to early civilizations, evolving into an extensive, organically based healthcare system, particularly in the Chinese culture[[81]. Interestingly, the use of herbal medicines in treating UC based on traditional Chinese medicine has significantly transformed over time [82]. This long continuum of use has allowed for the fine-tuning of these traditional methodologies to adapt and cater to the needs for patients with UC [83].

XI.CURRENT RESEARCH ON CHINESE MEDICINES

Current research has brought forward numerous herbal medicines that have shown promise in the treatment of ulcerative colitis [84]. Aloe Vera Gel, with its anti-inflammatory properties and ability to heal irritated tissues, has exhibited potential in reducing UC symptoms. Wheat Grass Juice, rich in antioxidants and nutrients, has demonstrated favorable outcomes in managing UC conditions [85]. Studies on Boswellia Serrata, an Ayurvedic herb with anti-inflammatory properties, also suggest its beneficial effects on UC [86]. Moreover, research on Bovine Colostrum Enemas indicates that colostrum may enhance gut immune function to ameliorate UC symptoms, presenting a compelling area for future investigation [87].

TCM is receiving widespread acknowledgment for the management of ulcerative colitis [88]. The mastery of TCM involves a combination of herbal remedies, acupuncture, and other therapeutic modalities, focusing on the correction of imbalances and restoration of homeostasis [89]. TCM therapy is respected for minimizing adverse drug reactions caused by conventional treatment approaches [90]. However, despite its effectiveness, it is also associated with certain drawbacks like a lack of consistent quality control among herbal medicines [91]. Clinical trials and evidence have advocated for TCM in UC treatment, with studies showing promising anti-inflammatory, immunomodulatory, and mucosal protective effects in UC management [92]. The evidence from clinical trials lays the foundation for emphasizing TCM as a beneficial alternative for treating UC, warranting further in-depth research to harness its full potential and integrate it seamlessly into conventional management practices [93].

Bioactivity of Herbs in Ulcerative Colitis Treatment

Understanding the profound bioactivity of herbs in the treatment of UC is critical. Herbs used in UC treatment encompass a wide range of bioactivities [94]. Clinical trials and experimental studies have been conducted to explore the potential effectiveness of these herbs in treating UC. These studies shed light on the underlying bioactivities exhibited by aloe vera gel, wheat grass juice, Boswellia serrate, and bovine colostrum enemas, as well as various other herbal therapies [95]. These findings contribute significantly to the assessment of the potential effectiveness of herbs in managing UC, depicting the comprehensive pool of herbs' bioactivity to pave the way for further development and understanding [96].

Clinical Efficacy of Herbal and Chinese Medicines

Several clinical studies have been conducted to assess the efficacy of herbal medicines in the management of UC [97]. These studies have been instrumental in producing a comprehensive summary of trials using herbal therapy for UC, shedding light on their clinical impact and patient adherence to these treatments. Research has also been dedicated to exploring patient adherence trends and the considerations for herbal treatment in UC, highlighting the multifaceted impacts of herbal medicines on patient well-being and outcome assessment [98]. Through these studies, evidence of the clinical efficacy of herbal medicines in UC treatment is being elucidated, paving the way for further exploration and understanding of their utilization and impact [99].

The bench-to-bedside approach for herbal medicines initiates with a comprehensive exploration of the bioactivities of these alternative treatment methods [100]. In the context of UC, integrating conventional Western treatments with traditional Chinese medicine and herbal remedies presents a promising and multifaceted approach to management [101]. TCM, particularly herbal medicines, exhibits potential when combined with standard treatment regimens, thus merging ancient practices with modern medicine to aid in UC management [102]. In summary, herbal medicines hold substantial potential within the UC treatment landscape, providing feasible clinical applications and a path for further exploration [103].

XII.ADVANTAGES AND CHALLENGES OF HERBAL AND CHINESE MEDICINES

The potential effectiveness of both herbal and Chinese medicines in the treatment of ulcerative colitis is an important metric to consider [104]. These treatments offer a relatively low-cost and high acceptance rate among patients, making them particularly attractive in disease management. However, coupled with these benefits, there are substantial safety and side effect concerns observed with herbal and Chinese medicines [105]. The limitations in implementing these treatments lie in the lack of standardization, quality control, and the potential for incorrect dosing or usage by individuals due to variable practices in traditional medicines. These medicines present a unique set of advantages and challenges, and understanding the effectiveness, safety, and implementation obstacles is crucial for their integration into ulcerative colitis treatment [106].

XIII.CONCLUSION

Ulcerative colitis presents a significant economic burden1 on the healthcare system, primarily due to the long-term nature of the treatment, the potential need for surgical interventions, and the management of side effects. The cost-effectiveness of different treatment options, including medication, dietary changes, and surgical interventions, plays a crucial role in addressing this burden. Adverse effects, hospitalizations, and medication costs require careful consideration to optimize resource allocation within healthcare systems. This emphasizes the need for research and strategies that aim to mitigate the economic impact while ensuring the delivery of effective and patient-centered care.

Identifying the current gaps in our understanding of ulcerative colitis and areas for future research is crucial for advancing treatment options. Continued investigation is essential for improving the efficacy and safety of available therapies. Moreover, ongoing research holds the potential for developing personalized and targeted treatment approaches. These individualized therapies can be tailored to each patient's specific condition, potentially leading to more effective and better-tolerated treatments.

The exploration of treatment approaches for ulcerative colitis illuminated the significance of tailored interventions to suit each patient's unique needs. Emphasizing the variability in individual responses, the importance of individualized treatment approaches cannot be overstated. Each patient's journey with ulcerative colitis is different, and it is crucial to consider this in treatment planning. Encouraging ongoing research and support is vital in advancing the understanding of this condition and improving treatment options. Through personalized approaches and continuous exploration, the future holds promise for more effective and targeted therapies tailored to the specific needs of each patient.

The standard approach to treating UC primarily involves medications to manage inflammation or control symptoms; however, herbal and Chinese medicines can offer an alternative, complementary strategy. The review has elucidated that herbal and Chinese medicines are not only associated with potential therapeutic benefits but could also foster improved patient adherence, better tolerability, safety, and cost-effectiveness. By being aware of the advantages and challenges of herbal and Chinese medicines, healthcare practitioners can offer more comprehensive treatment options for UC patients to enhance their overall well-being.

In summary, UC remains a challenging global disease with ambiguous pathogenesis and considerable unmet needs regarding optimal therapeutic selection and delivery. Confronting rising epidemiological trends will require dedicated research efforts focused on unravelling disease triggers alongside piloting innovative personalized treatments to ultimately mitigate escalating disease burden.

REFERENCES:

1. Colitis-Pathophysiology U. Inflammatory bowel disease part I: ulcerative colitis-pathophysiology and conventional and alternative treatment options. Altern Med Rev. 2003;8(3):247-83.
2. Rubin RR, Peyrot M. Psychological issues and treatments for people with diabetes. Journal of clinical psychology. 2001 Apr;57(4):457-78.
3. Preda CM, Istrătescu D. Etiology of Ulcerative Colitis. InUlcerative Colitis-Etiology, Diagnosis, Diet, Special Populations, and the Role of Interventional Endoscopy 2022 Sep 1. IntechOpen.
4. Baldi F, Bianco MA, Nardone G, Pilotto A, Zamparo E. Focus on acute diarrhoeal disease. World journal of gastroenterology: WJG. 2009 Jul 7;15(27):3341.
5. Satsangi J, Silverberg MS, Vermeire S, Colombel J. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut. 2006 Jun 1;55(6):749-53.
6. Kaur A, Goggolidou P. Ulcerative colitis: understanding its cellular pathology could provide insights into novel therapies. Journal of inflammation. 2020 Dec; 17:1-8.
7. Otte ML, Tamang RL, Papapanagiotou J, Ahmad R, Dhawan P, Singh AB. Mucosal healing and inflammatory bowel disease: Therapeutic implications and new targets. World Journal of Gastroenterology. 2023 Feb 2;29(7):1157.
8. Vebr M, Pomahačová R, Sýkora J, Schwarz J. A Narrative Review of Cytokine Networks: Pathophysiological and Therapeutic Implications for Inflammatory Bowel Disease Pathogenesis. Biomedicines. 2023 Dec 6;11(12):3229.
9. Liang A, Kong Y, Chen Z, Qiu Y, Wu Y, Zhu X, Li Z. Advancements and applications of single-cell multi-omics techniques in cancer research: Unveiling heterogeneity and paving the way for precision therapeutics. Biochemistry and Biophysics Reports. 2024 Mar 1;37:101589.
10. Byron C, Cornally N, Burton A, Savage E. Challenges of living with and managing inflammatory bowel disease: A meta-synthesis of patients' experiences. Journal of clinical nursing. 2020 Feb;29(3-4):305-19.
11. Aquino CC, Fox SH. Clinical spectrum of levodopa-induced complications. Movement Disorders. 2015 Jan;30(1):80-9.
12. McIntyre RS, Alda M, Baldessarini RJ, Bauer M, Berk M, Correll CU, Fagiolini A, Fountoulakis K, Frye MA, Grunze H, Kessing LV. The clinical characterization of the adult patient with bipolar disorder aimed at personalization of management. World Psychiatry. 2022 Oct;21(3):364-87.
13. Buie MJ, Quan J, Windsor JW, Coward S, Hansen TM, King JA, Kotze PG, Gearry RB, Ng SC, Mak JW, Abreu MT. Global hospitalization trends for crohn's disease and ulcerative colitis in the 21st century: a systematic review with temporal analyses. Clinical gastroenterology and hepatology. 2023 Aug 1;21(9):2211-21.
14. Barreiro-de Acosta M, Molero A, Artime E, Díaz-Cerezo S, Lizán L, de Paz HD, Martín-Arranz MD. Epidemiological, Clinical, Patient-Reported and Economic Burden of Inflammatory Bowel Disease (Ulcerative colitis and Crohn's disease) in Spain: A Systematic Review. Advances in Therapy. 2023 May;40(5):1975-2014.
15. Rogers MA, Kim C, Banerjee T, Lee JM. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. BMC medicine. 2017 Dec; 15:1-9.
16. Ng SC, Bernstein CN, Vatn MH, Lakatos PL, Loftus EV, Tysk C, O'Morain C, Moum B, Colombel JF. Geographical variability and environmental risk factors in inflammatory bowel disease. Gut. 2013 Apr 1;62(4):630-49.
17. Rehle T, Lazzari S, Dallabetta G, Asamoah-Odei E. Second-generation HIV surveillance: better data for decision-making. Bulletin of the World Health Organization. 2004; 82:121-7.
18. Thompson AI, Lees CW. Genetics of ulcerative colitis. Inflammatory bowel diseases. 2011 Mar 1;17(3):831-48.
19. El Hadad J, Schreiner P, Vavricka SR, Greuter T. The Genetics of Inflammatory Bowel Disease. Molecular Diagnosis & Therapy. 2023 Oct 17:1-9.
20. Keely S, Walker MM, Marks E, Talley NJ. Immune dysregulation in the functional gastrointestinal disorders. European journal of clinical investigation. 2015 Dec;45(12):1350-9.
21. Barbara G, Barbaro MR, Fuschi D, Palombo M, Falangone F, Cremon C, Marasco G, Stanghellini V. Inflammatory and microbiota-related regulation of the intestinal epithelial barrier. Frontiers in Nutrition. 2021 Sep 13; 8:718356.
22. Ibrahim CB, Aroniadis OC, Brandt LJ. On the role of ischemia in the pathogenesis of IBD: a review. Inflammatory bowel diseases. 2010 Apr 1;16(4):696-702.
23. Trivedi PJ, Adams DH. Mucosal immunity in liver autoimmunity: a comprehensive review. Journal of autoimmunity. 2013 Oct 1; 46:97-111.

24. Lamb CA, Saifuddin A, Powell N, Rieder F. The future of precision medicine to predict outcomes and control tissue remodeling in inflammatory bowel disease. Gastroenterology. 2022 Apr 1;162(5):1525-42.
25. Jobin C, Sartor BR. NF-κB signaling proteins as therapeutic targets for inflammatory bowel diseases. Inflammatory bowel diseases. 2000 Aug 1;6(3):206-13.
26. Yao D, Dong M, Dai C, Wu S. Inflammation and inflammatory cytokine contribute to the initiation and development of ulcerative colitis and its associated cancer. Inflammatory bowel diseases. 2019 Sep 18;25(10):1595-602.
27. Coskun M, Salem M, Pedersen J, Nielsen OH. Involvement of JAK/STAT signaling in the pathogenesis of inflammatory bowel disease. Pharmacological research. 2013 Oct 1;76:1-8.
28. The activated STAT proteins translocate to the nucleus and induce the expression of inflammatory genes. Targeting JAKs with specific inhibitors has shown promise in dampening the inflammatory response and has emerged as a therapeutic strategy for UC.
29. Samoilă I, Dinescu S, Costache M. Interplay between cellular and molecular mechanisms underlying inflammatory bowel diseases development—a focus on ulcerative colitis. Cells. 2020 Jul 9;9(7):1647.
30. Tatiya-Aphiradee N, Chatuphonprasert W, Jarukamjorn K. Immune response and inflammatory pathway of ulcerative colitis. Journal of basic and clinical physiology and pharmacology. 2018 Dec 19;30(1):1-0.
31. Deng F, Peng L, Li Z, Tan G, Liang E, Chen S, Zhao X, Zhi F. YAP triggers the Wnt/β-catenin signalling pathway and promotes enterocyte self-renewal, regeneration and tumorigenesis after DSS-induced injury. Cell death & disease. 2018 Feb 2;9(2):153.
32. Kordjazy N, Haj-Mirzaian A, Haj-Mirzaian A, Rohani MM, Gelfand EW, Rezaei N, Abdolghaffari AH. Role of toll-like receptors in inflammatory bowel disease. Pharmacological Research. 2018 Mar 1;129:204-15.
33. Uribe G. Protective Role of Mesenchymal MyD88 Signaling Under Homeostasis and Initiation of Inflammation in the Colon (Doctoral dissertation).
34. Mohseni AH, Casolaro V, Bermúdez-Humarán LG, Keyvani H, Taghinezhad-S S. Modulation of the PI3K/Akt/mTOR signaling pathway by probiotics as a fruitful target for orchestrating the immune response. Gut Microbes. 2021 Jan 1;13(1):1886844.
35. Yu L, Zhang MM, Hou JG. Molecular and cellular pathways in colorectal cancer: apoptosis, autophagy and inflammation as key players. Scandinavian Journal of Gastroenterology. 2022 Nov 2;57(11):1279-90.
36. Ananthakrishnan AN, Xavier RJ, Podolsky DK. Inflammatory bowel diseases: a clinician's guide. John Wiley & Sons; 2017 Apr 24.
37. Smith SC. Advanced endoscopic techniques and optical diagnosis in the lower gastrointestinal tract (Doctoral dissertation, University of Birmingham).
38. Jiang Y, Wang C, Zhou S. Artificial intelligence-based risk stratification, accurate diagnosis and treatment prediction in gynaecologic oncology. InSeminars in Cancer Biology 2023 Sep 30. Academic Press.
39. Gajendran M, Loganathan P, Jimenez G, Catinella AP, Ng N, Umapathy C, Ziade N, Hashash JG. A comprehensive review and update on ulcerative colitis. Disease-a-month. 2019 Dec 1;65(12):100851.
40. Gorecki C, Nixon J, Madill A, Firth J, Brown JM. What influences the impact of pressure ulcers on health-related quality of life? A qualitative patient-focused exploration of contributory factors. Journal of tissue viability. 2012 Feb 1;21(1):3-12.
41. Apovian CM, Garvey WT, Ryan DH. Challenging obesity: Patient, provider, and expert perspectives on the roles of available and emerging nonsurgical therapies. Obesity. 2015 Jul;23:S1-26.
42. Singh S, Allegretti JR, Siddique SM, Terdiman JP. AGA technical review on the management of moderate to severe ulcerative colitis. Gastroenterology. 2020 Apr 1;158(5):1465-96.
43. Fakhoury M, Negrulj R, Mooranian A, Al-Salami H. Inflammatory bowel disease: clinical aspects and treatments. Journal of inflammation research. 2014 Jun 23:113-20.
44. Floris A, Piga M, Chessa E, Congia M, Erre GL, Angioni MM, Mathieu A, Cauli A. Long-term glucocorticoid treatment and high relapse rate remain unresolved issues in the real-life management of polymyalgia rheumatica: a systematic literature review and meta-analysis. Clinical Rheumatology. 2022 Jan;41(1):19-31.
45. Beiranvand M. A review of the biological and pharmacological activities of mesalazine or 5-aminosalicylic acid (5-ASA): an anti-ulcer and anti-oxidant drug. Inflammopharmacology. 2021 Oct;29(5):1279-90.
46. Lahad A, Weiss B. Current therapy of pediatric Crohn's disease. World journal of gastrointestinal pathophysiology. 2015 May 5;6(2):33.
47. Greenfield SM, Punchard NA, Teare JP, Thompson RP. The mode of action of the aminosalicylates in inflammatory bowel disease. Alimentary pharmacology & therapeutics. 1993 Aug;7(4):369-83.
48. Linares V, Alonso V, Domingo JL. Oxidative stress as a mechanism underlying sulfasalazine-induced toxicity. Expert opinion on drug safety. 2011 Mar 1;10(2):253-63.

49. Leporini C, De Sarro G, Russo E. Adherence to therapy and adverse drug reactions: is there a link?. Expert opinion on drug safety. 2014 Sep 1;13(sup1):41-55.
50. Beiranvand M. A review of the biological and pharmacological activities of mesalazine or 5-aminosalicylic acid (5-ASA): an anti-ulcer and anti-oxidant drug. Inflammopharmacology. 2021 Oct;29(5):1279-90.
51. Toshifumi HI. Pathogenesis and treatment of ulcerative colitis. JMA Policies. 2003;257.
52. Behrens A, Doyle JJ, Stern L, Chuck RS, McDonnell PJ, Azar DT, Dua HS, Hom M, Karpecki PM, Laibson PR, Lemp MA. Dysfunctional tear syndrome: a Delphi approach to treatment recommendations. Cornea. 2006 Sep 1;25(8):900-7.
53. Nayar M, Rhodes JM. Management of inflammatory bowel disease. Postgraduate medical journal. 2004 Apr;80(942):206-13.
54. Seah D, De Cruz P. the practical management of acute severe ulcerative colitis. Alimentary pharmacology & therapeutics. 2016 Feb;43(4):482-513.
55. Akobeng AK, Zhang D, Gordon M, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. Cochrane database of systematic reviews. 2016(9).
56. Sinusas K. Osteoarthritis: diagnosis and treatment. American family physician. 2012 Jan 1;85(1):49-56.
57. Jeetu G, Anusha G. Pharmacovigilance: a worldwide master key for drug safety monitoring. Journal of Young Pharmacists. 2010 Jul 1;2(3):315-20.
58. Sydnor ER, Perl TM. Hospital epidemiology and infection control in acute-care settings. Clinical microbiology reviews. 2011 Jan;24(1):141-73.
59. Stange EF. Current and future aspects of IBD research and treatment: the 2022 perspective. Frontiers in Gastroenterology. 2022 Aug 11; 1:914371.
60. Smolen JS, Landewé RB, Bijlsma JW, Burmester GR, Dougados M, Kerschbaumer A, McInnes IB, Sepriano A, Van Vollenhoven RF, De Wit M, Aletaha D. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Annals of the rheumatic diseases. 2020 Jun 1;79(6):685-99.
61. Quezada SM, McLean LP, Cross RK. Adverse events in IBD therapy: the 2018 update. Expert Review of Gastroenterology & Hepatology. 2018 Dec 2;12(12):1183-91.
62. Köhler LW, Pemberton JH, Zinsmeister AR, Kelly KA. Quality of life after proctocolectomy: a comparison of Brooke ileostomy, Kock pouch, and ileal pouch-anal anastomosis. Gastroenterology. 1991 Sep 1;101(3):679-84.
63. Hueting WE, Buskens E, Van Der Tweel I, Gooszen HG, van Laarhoven CJ. Results and complications after ileal pouch anal anastomosis: a meta-analysis of 43 observational studies comprising 9,317 patients. Digestive surgery. 2005 May 11;22(1-2):69-79.
64. Barry CA, Stevenson FA, Britten N, Barber N, Bradley CP. Giving voice to the lifeworld. More humane, more effective medical care? A qualitative study of doctor–patient communication in general practice. Social science & medicine. 2001 Aug 1;53(4):487-505.
65. Algorri M, Cauchon NS, Christian T, O'Connell C, Vaidya P. Patient-Centric product development: a summary of select regulatory CMC and device considerations. Journal of Pharmaceutical Sciences. 2023 Apr 1;112(4):922-36.
66. Ungaro R, Colombel JF, Lissoos T, Peyrin-Biroulet L. A treat-to-target update in ulcerative colitis: a systematic review. The American journal of gastroenterology. 2019 Jun;114(6):874.
67. Mohamad T, Jyotsna FN, Farooq U, Fatima A, Kar I, Khuwaja S, Memon UA, Kumari V, Puri P, Aslam ZM, Elder Z. Individualizing medicinal therapy post heart stent implantation: tailoring for patient factors. Cureus. 2023 Aug 23;15(8).
68. Sugandh FN, Chandio M, Raveena FN, Kumar L, Karishma FN, Khuwaja S, Memon UA, Bai K, Kashif M, Varrassi G, Khatri M. Advances in the management of diabetes mellitus: a focus on personalized medicine. Cureus. 2023 Aug 18;15(8).
69. Armuzzi A, Liguori G. Quality of life in patients with moderate to severe ulcerative colitis and the impact of treatment: a narrative review. Digestive and Liver Disease. 2021 Jul 1;53(7):803-8.
70. Halmos EP, Gibson PR. Dietary management of IBD—insights and advice. Nature Reviews Gastroenterology & Hepatology. 2015 Mar;12(3):133-46.
71. Vanhauwaert E, Matthys C, Verdonck L, De Preter V. Low-residue and low-fiber diets in gastrointestinal disease management. Advances in Nutrition. 2015 Nov;6(6):820-7.
72. Muthukumar J, Selvasekaran P, Lokanadham M, Chidambaram R. Food and food products associated with food allergy and food intolerance–An overview. Food Research International. 2020 Dec 1;138:109780.
73. Richman E, Rhodes JM. evidence-based dietary advice for patients with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2013 Nov;38(10):1156-71.

74. D'Haens G. Risks and benefits of biologic therapy for inflammatory bowel diseases. Gut. 2007 May 1;56(5):725-32.
75. Helavirta I. Restorative Proctocolectomy and Ileal Pouch-Anal Anastomosis for Ulcerative Colitis.
76. Šitum M, Franceschi D, Franceschi N. Challenges and strategies in dermatologic therapy—Personalized medicine, patient safety, and pharmacoeconomics. Dermatologic Therapy. 2019 Jul;32(4):e13011.
77. Liu CY, Cham CM, Chang EB. Epithelial wound healing in inflammatory bowel diseases: the next therapeutic frontier. Translational Research. 2021 Oct 1;236:35-51.
78. Mitra AK, Agrahari V, Mandal A, Cholkar K, Natarajan C, Shah S, Joseph M, Trinh HM, Vaishya R, Yang X, Hao Y. Novel delivery approaches for cancer therapeutics. Journal of controlled release. 2015 Dec 10;219:248-68.
79. Ungaro R, Colombel JF, Lissoos T, Peyrin-Biroulet L. A treat-to-target update in ulcerative colitis: a systematic review. The American journal of gastroenterology. 2019 Jun;114(6):874.
80. Swaroop AK, Negi P, Kar A, Mariappan E, Natarajan J, PK KN, Selvaraj J. Navigating IL-6: From molecular mechanisms to therapeutic breakthroughs. Cytokine & Growth Factor Reviews. 2024 Jan 2.
81. Gupta JK, Singh AP, Sharma Y. Exploring Chinese Herbal Medicine for the Treatment of Inflammatory Bowel Disease: A Comprehensive Overview. Pharmacological Research-Modern Chinese Medicine. 2024 Feb 2:100380.
82. Hong H. Principles of Chinese medicine: A modern interpretation. World Scientific; 2015 Jul 15.
83. Ke F, Yadav PK, Ju LZ. Herbal medicine in the treatment of ulcerative colitis. Saudi journal of gastroenterology: official journal of the Saudi Gastroenterology Association. 2012 Jan;18(1):3.
84. Hinrichs TJ, Barnes LL, editors. Chinese Medicine and Healing: an illustrated history. Harvard University Press; 2013 Jan 7.
85. Sałaga M, Zatorski H, Sobczak M, Chen C, Fichna J. Chinese herbal medicines in the treatment of IBD and colorectal cancer: a review. Current treatment options in oncology. 2014 Sep;15:405-20.
86. Mangiron C. Found in translation: evolving approaches for the localization of japanese video games. InArts 2021 Jan 26 (Vol. 10, No. 1, p. 9). MDPI.
87. Meineri G, Martello E, Radice E, Bruni N, Saettone V, Atuahene D, Armandi A, Testa G, Ribaldone DG. Chronic Intestinal Disorders in Humans and Pets: Current Management and the Potential of Nutraceutical Antioxidants as Alternatives. Animals. 2022 Mar 23;12(7):812.
88. Hartmann RM, Fillmann HS, Morgan Martins MI, Meurer L, Marroni NP. Boswellia serrata has beneficial anti-inflammatory and antioxidant properties in a model of experimental colitis. Phytotherapy research. 2014 Sep;28(9):1392-8.
89. Chandwe K, Kelly P. Colostrum therapy for human gastrointestinal health and disease. Nutrients. 2021 Jun 7;13(6):1956.
90. Kou FS, Shi L, Li JX, Wang ZB, Shi R, Mao TY, Ke X, Zhang BP, Yang XJ, Wen XL, Zheng WY. Clinical evaluation of traditional Chinese medicine on mild active ulcerative colitis: A multi-center, randomized, double-blind, controlled trial. Medicine. 2020 Aug 8;99(35).
91. Diamond WJ. The clinical practice of complementary, alternative, and Western medicine. CRC Press; 2000 Sep 26.
92. Chan K, Zhang H, Lin ZX. An overview on adverse drug reactions to traditional Chinese medicines. British journal of clinical pharmacology. 2015 Oct;80(4):834-43.
93. Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Brazilian Journal of medical and Biological research. 2000;33:179-89.
94. Bai Y, Qiao Y, Li M, Yang W, Chen H, Wu Y, Zhang H. RIPK1 inhibitors: A key to unlocking the potential of necroptosis in drug development. European Journal of Medicinal Chemistry. 2024 Jan 3:116123.
95. Abdel-Tawab M. Considerations to be taken when carrying out medicinal plant research—what we learn from an insight into the IC50 values, bioavailability and clinical efficacy of exemplary anti-inflammatory herbal components. Pharmaceuticals. 2021 May 6;14(5):437.
96. Ungaro R, Colombel JF, Lissoos T, Peyrin-Biroulet L. A treat-to-target update in ulcerative colitis: a systematic review. The American journal of gastroenterology. 2019 Jun;114(6):874.
97. Zhu MZ, Yang MF, Song Y, Xu HM, Xu J, Yue NN, Zhang Y, Tian CM, Shi RY, Liang YJ, Yao J. Exploring the efficacy of herbal medicinal products as oral therapy for inflammatory bowel disease. Biomedicine & Pharmacotherapy. 2023 Sep 1;165:115266.
98. Cooper R, Kronenberg F, editors. Botanical medicine: from bench to bedside. Mary Ann Liebert, Inc., publishers; 2009.

99. Hu Y, Ye Z, She Y, Li L, Wu M, Qin K, Li Y, He H, Hu Z, Yang M, Lu F. Efficacy and safety of probiotics combined with traditional Chinese medicine for ulcerative colitis: A systematic review and meta-analysis. Frontiers in pharmacology. 2022 Mar 7;13:844961.
100. Chen J, Shen B, Jiang Z. Traditional Chinese medicine prescription Shenling BaiZhu powder to treat ulcerative colitis: Clinical evidence and potential mechanisms. Frontiers in Pharmacology. 2022 Sep 6;13:978558.
101. Bulcha JT, Wang Y, Ma H, Tai PW, Gao G. Viral vector platforms within the gene therapy landscape. Signal transduction and targeted therapy. 2021 Feb 8;6(1):53.
102. Zhang C, Jiang M, Lu A. Considerations of traditional Chinese medicine as adjunct therapy in the management of ulcerative colitis. Clinical reviews in allergy & immunology. 2013 Jun;44:274-83.
103. Schuitmaker JJ, Baas P, Van Leengoed HL, Van der Meulen FW, Star WM, van Zandwijk N. Photodynamic therapy: a promising new modality for the treatment of cancer. Journal of Photochemistry and Photobiology B: Biology. 1996 Jun 1;34(1):3-12.
104. Ernst E. Herbal medicines: balancing benefits and risks. InDietary Supplements and Health: Novartis Foundation Symposium 282 2007 Jul 27 (Vol. 282, pp. 154-172). Chichester, UK: John Wiley & Sons, Ltd.
105. Kunle, Oluyemisi F, Egharevba, Henry O, Ahmadu, Peter O. Standardization of herbal medicines-A review. International journal of biodiversity and conservation. 2012 Mar 31;4(3):101-12.
106. Yeshi K, Ruscher R, Hunter L, Daly NL, Loukas A, Wangchuk P. Revisiting inflammatory bowel disease: pathology, treatments, challenges and emerging therapeutics including drug leads from natural products. Journal of clinical medicine. 2020 Apr 28;9(5):1273.