Explores 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].
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.

**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. 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 burden 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.


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