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Contents

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EDITORIAL

CASE REPORT

LETTER TO THE EDITOR

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Contents

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LETTER TO THE EDITOR

Optimal traditional Chinese medicine formulas in treating ulcerative colitis: Choose one or take it all?

Yan Zeng, Jun-Wen Zhang, Jian Yang

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Yan Zeng, Department of Psychology, The Second Affiliated Hospital of Chongqing Medical University, Chongqing 400010, China

Jun-Wen Zhang, Jian Yang, Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

Corresponding author: Jian Yang, MD, PhD, Associate Chief Physician, Department of Gastroenterology, The First Affiliated Hospital of Chongqing Medical University, No. 1 Youyi Road, Yuzhong District, Chongqing 400016, China. yangjian@hospital.cqmu.edu.cn

Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that presents significant treatment challenges due to its complexity, especially in terms of the various side effects that traditional medications may bring during the chronic course of the disease. Traditional Chinese medicine (TCM) has emerged as a promising complementary therapy for UC. Based on the latest research, our editorial explored the current issues and potential essential research directions for TCM in treating UC. We anticipate that future high-quality research will pave the way for the optimization of TCM formulas for UC and their broader global application.

Key Words: Traditional Chinese medicine; Ulcerative colitis; Inflammatory bowel disease; Formula; Treatment

Core Tip: Traditional Chinese medicine (TCM) offers a promising approach to treating ulcerative colitis, a chronic inflammatory bowel disease that can be challenging to manage with conventional medical therapies. Exploring the optimal TCM formulas, addressing the concerns surrounding its efficacy, safety, standardization, and mode of action, and improving the quality of clinical research are all crucial for the wider acceptance and integration of TCM into global medical practice.

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TO THE EDITOR

Ulcerative colitis (UC) is a chronic inflammatory bowel disease that poses significant challenges in its treatment due to its complex nature. The condition involves large intestine and rectum inflammation, leading to symptoms such as abdominal pain, diarrhea, and mucopurulent bloody stools[1]. Traditional Western medical treatments, such as salicylates, glucocorticoids, anti-inflammatory drugs, and immunosuppressants, are effective in managing the symptoms but often come with side effects and may not address the underlying causes of the disease[2,3].

Given these constraints, traditional Chinese medicine (TCM) has emerged as a promising complementary therapy for UC. TCM adopts a holistic and individualized approach to health and disease, focusing on restoring balance and harmony within the body. TCM treatments for UC may include acupuncture, herbal remedies, and dietary modifications [4,5]. In TCM research for UC, we have noted a forthcoming study[6]. The authors have comprehensively analyzed and compared the efficacy of five TCM formulas approved by the Chinese State Drug Administration for treating UC[6]. This research provides a scientific basis for clinical decision-making regarding use of TCM as an adjuvant therapy for UC. Based on this study, this editorial focused on current concerns and potential directions for developing TCM formulas in treating UC. We aimed to promote the research and application of TCM formulas in more regions and strive for better treatment outcomes.

CONCERNS ABOUT TCM FORMULAS

Reference Citation Analysis (referred to as *RCA*; https://www.referencecitationanalysis.com/) is a unique artificial intelligence system for evaluating citations in biomedical literature. *RCA* has been employed to analyze previous studies of TCM formulas for UC up to June 2024. The following may be some of the hot-button issues currently being discussed in the research on TCM in the treatment of UC.

Efficacy and safety

The efficacy and mechanism of TCM formulations in treating UC is a primary concern. TCM considers dampness-heat to be the primary pathogenic mechanism of UC. Therefore, TCM treatment for UC is performed under the guidance of theories such as "clearing heat and eliminating dampness"[7]. While some studies have suggested positive outcomes, the evidence supporting the efficacy of TCM in UC treatment is often limited, and it mainly comes from studies conducted by Chinese scholars[8]. For example, the Baitouweng decoction (BD) as discussed in the research of Zhao *et al*[6] was first detailed in Treatise on Febrile Diseases, written by the renowned Chinese physician Zhang Zhongjing in the early 3rd century AD[9]. The main components of BD are Pulsatilla chinensis (Bunge) Regel, Coptis chinensis Franch, Phellodendron chinense Schneid, and Cortex Fraxini[6,9].

Among the primary components of BD, Coptis chinensis Franch has a history of several hundred years in treating gastrointestinal disorders, including ulcers and inflammation, for several centuries. Recent studies have proposed that it may prevent intestinal barrier damage by regulating gut microbiota imbalances and inhibiting inflammatory responses [10]. Meanwhile, Dihydroberberine, found in TCM like Coptis chinensis Franch and Phellodendron chinense Schneid, which are commonly used to treat colitis, has been shown to exert beneficial effects similar to those of azathioprine and improves intestinal barrier function and ameliorates the colonic immune-inflammatory state[11]. Another critical component of BD, Pulsatilla chinensis (Bunge) Regel, is capable of increasing the content of short-chain fatty acids in colonic tissues through its active ingredient, Pulsatilla chinensis saponin, which activates the GPR43-NLRP3 signaling pathway and reduces levels of proinflammatory cytokines, thereby alleviating symptoms of colitis[12].

Recent research on TCM and its impact on gut microbiota has revealed that TCM can regulate immunity and gut microbiota by modulating intestinal microecology. TCM can effectively increase the abundance of beneficial bacteria producing short-chain fatty acids, reduce the abundance of pathogenic bacteria, restore the balance of gut microbiota, and alleviate intestinal mucosal immune barrier dysfunction, thereby promoting the repair of damaged colorectal mucosa [13]. Building on this research, some scholars have combined TCM with fecal microbiota transplantation to treat UC and have observed significant improvements in the diversity and abundance of gut microbiota following treatment[14].

In addition to the studies mentioned above, there has been an increasing amount of research in recent years exploring the mechanisms of TCM formulas, such as the relationship between ferroptosis and "dampness-heat"[7,15]. The exact mechanisms of TCM in treating UC have not been fully elucidated, which poses challenges for scientifically assessing the efficacy of TCM. Additionally, the variability in the composition of TCM formulas due to differences in herb sourcing, preparation methods, and concentrations further complicates the evaluation of their efficacy and mechanism. These concerns also raise whether using single TCM or TCM formulas in UC treatment is recommended. Given the complexity of inflammatory bowel disease, its pathogenesis involves many dynamic interactions between components at different functional levels. Therefore, in future explorations of the mechanisms of TCM in treating UC and in addressing how to

optimize between single TCM and TCM formulas, a more systemic approach from the perspective of the network of all components of the inflammatory bowel diseases interactome can be considered[16].

Safety is another significant concern associated with TCM treatments for UC. The wide range of ingredients in TCM formulas, many of which are not well-characterized or standardized, can lead to unpredictable effects[17]. Moreover, the potential for TCM formulations to interact with conventional medications used in UC treatment is not well-documented, raising concerns about the safety of concurrent use. Without comprehensive data on these interactions, healthcare providers may hesitate to recommend TCM as an adjunct therapy for UC, especially for patients on complex medication regimens. Therefore, further exploration of the safety of combining TCM with commonly used drugs for UC treatment is also one of the promising research directions in the future.

Standardization and quality control

One major challenge in TCM research is the lack of standardization in formulations. Herbal ingredients can vary in quality and potency, which can be influenced by factors such as the source of the herbs, the growing conditions, the harvesting time, and the processing methods[18]. The absence of standardized manufacturing processes further complicates the issue, making it challenging to replicate study results and ensure consistency across different batches of the same formula. Quality control and assurance are essential in TCM research to ensure the consistency and safety of the formulations, which involves establishing stringent standards for the sourcing, preparing, and storing herbal ingredients and standardized manufacturing processes[19]. By ensuring the standardization of TCM formulas, researchers can more accurately assess their efficacy and safety, and healthcare providers can make more informed decisions about using TCM in treating UC[20].

TCM formulas can be composed of a single herb or a combination of multiple herbs, and the diversity and variability of these formulations present practical dilemmas in real-world decisions. As Zhao *et al*[6] found in their study, five commonly used TCM formulas have their own advantages in improving tumor necrosis factor levels, quality of life, colonoscopy scores, and recurrence rates in UC patients. However, the recovery of UC patients is not just about one aspect mentioned above but more about seeking overall improvement in various aspects. From the perspective of this treatment goal, should it be recommended to use a combination of the above formulas or to obtain relatively better results by optimizing a particular formula? If the latter is chosen, individualized optimization of the formula based on different disease severity and treatment goals may be one of the future research directions.

Mode of action

The commonly used TCM administration methods for patients with UC are oral and enema. Due to poor water solubility and instability of TCM, its widespread clinical application is challenged. Fortunately, the development of novel drug delivery systems in recent years has led to the emergence of various new methods for encapsulating therapeutic drugs, including exosomes, nanoemulsions, nanospheres, nanotubes, solid lipid nanoparticles, and lipid-based nanocarriers, providing new feasible approaches for TCM treatment of UC or symptom relief[21,22].

The current issue is that the novel drug delivery methods encapsulating TCM are still far from being used in real-world patient care. Additionally, whether it is possible to recombine the TCM components that play a significant role in the overall treatment goals of patients during the development of new drug delivery systems for TCM, thereby creating innovative TCM formulas for UC patients, may also be a question worth exploring.

In addition to the concerns discussed above, further research is still needed to determine the best TCM treatment options for patients with UC, whether Chinese medicine monomers, single Chinese medicines, or TCM formulas. After all, optimizing the types and quantities of TCM used in treating UC can help reduce adverse reactions while ensuring efficacy, but this depends on in-depth research into the mechanisms of action of currently commonly used TCM formulas. During the research process, it is also necessary to be aware of the limitations similar to other TCM research, such as relatively fewer clinical studies, many of which have limitations in method design and outcome quality. More rigorous, well-designed clinical trials are still needed to determine the efficacy and safety of TCM in treating UC[23].

CONCLUSION

The apprehensions surrounding TCM therapy for UC not only highlight existing challenges but also suggest numerous avenues for future research and advancement. In a global landscape where inflammatory bowel diseases, including UC, have emerged as a focal point of scholarly inquiry and discourse, TCM is poised to provide novel insights and therapeutic modalities to enhance patient outcomes and strive towards ultimate "disease clearance".

FOOTNOTES

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Country of origin: China

ORCID number: Yan Zeng 0000-0003-4935-1306; Jun-Wen Zhang 0000-0003-2911-598X; Jian Yang 0000-0001-8170-0727.

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