Oral Nano-Delivery Systems for Colon-Targeted Drug Delivery of Traditional Chinese Medicine in Ulcerative Colitis

Mohammad Javed Ansari1*, Suhad J. Hadi2, Hamzah H. Kzar2, Moaded E. Al-Gazally3, Thufeqar Ahmed Hamza4, Mohammed Khudair Hasan5, Aiman Mohammed Baqir Al-Dhalimy6, Reza Akhavan-Sigari7,8

1Department of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-kharj, Saudi Arabia.
2Veterinary Medicine College, Al-Qasim Green University, Al-Qasim, Iraq.
3College of Medicine, University of Al-Ameed, Karbala, Iraq.
4Medical Laboratory Techniques Department, Al-Mustaqbal University College, Babylon, Iraq.
5Al-Manara College of Medical sciences, Department of Pharmacy, Missan, Iraq.
6College of Nursing, Al-Tosisi University College, Najaf, Iraq and The Islamic University, Najaf, Iraq.
7Department of Neurosurgery, University Medical Center Tuebingen, Germany.
8Department of Health Care Management and Clinical Research, Collegium Humanum Warsaw Management University Warsaw, Poland.

Corresponding author: javedpharma@gmail.com

Abstract: Ulcerative colitis (UC) is a type of inflammatory bowel disease with a high recurrence rate. In this regard, sulfasalazine and immunosuppressive medications are often used for an extended period in clinical practice, but their effectiveness is limited, and they are prone to side effects. Modern research has shown that herbal active ingredients of Traditional Chinese Medicine (TCM), such as polyphenols, alkaloids, quinones, and terpenes, have a promising impact on treating UC via a multi-target mechanism and with low side effects. Poor water solubility and low bioavailability of these agents in the gastrointestinal tract are the most challenging issues in delivering these agents to the target tissues. Researchers have created a variety of oral colon-targeted nano-systems of TCM active ingredients in response to the above formulation issues, which significantly improve the treatment of UC by avoiding gastrointestinal damage, prolonging intestinal retention, and achieving controlled drug release at the lesion site. In order to provide ideas for the oral-targeted treatment of UC with active ingredients from TCM, the research progress of an oral colon-targeted nano-system for the treatment of UC is reviewed in the current study, as well as the research progress of an oral colon-targeted nano-system for the treatment of UC.

Key words: Medicine, Chinese Traditional, Colitis, Ulcerative, Nanoparticle Drug Delivery System.

Introduction

Ulcerative colitis (UC) is a non-specific inflammatory bowel disease with a long course and is difficult to cure. The diseased area can reach the submucosa of the rectum, involving the rectum, sigmoid colon, and even the entire colon area1. Its clinical manifestations include abdominal pain, diarrhea, weight loss, and blood in the stool, which can be repeated. The World Health Organization has listed it as one of the modern refractory diseases. Its pathogenesis is complicated and related to increased mucosal permeability, imbalance of microbial levels, and tumor necrosis. Factor-α (tumor necrosis factor-α, TNF-α), interleukin-6 (interleukin-6, IL-6), interleukin-10 (interleukin-10, IL-10), and other factors related to the imbalance of the level of inflammatory factors2. Currently, the commonly used drugs for treating UC include 5-aminosalicylic acid, cortisol, and immunosuppressive drugs, but long-term use of these drugs can cause serious adverse reactions. According to the symptoms of the disease, UC belongs to the categories of "rest dysentery," "long dysentery," and "intestinal addiction" in Chinese medicine3. Based on the concept of syndrome differentiation and treatment, traditional Chinese medicine has a long history of preventing and treating UC, with significant clinical effects and minor adverse reactions. The treatment of UC with traditional Chinese medicine has the advantages of multiple components, multiple targets, and improvement of the internal environment. However, when the active ingredients of traditional Chinese medicine are treated orally, there are disadvantages, such as poor water solubility, low gastrointestinal stability, and poor oral bioavailability. How to achieve high-efficiency delivery of active ingredients of traditional Chinese medicine in colon lesions is a problem that needs to be solved urgently. This article summarizes the representative active ingredients of traditional Chinese medicines with the prevention and treatment effects on UC and their mechanism of action, as well as the research progress of oral colon-targeted nano-system for treating UC by consulting the Chinese and English literature in recent years.

Active ingredients of traditional Chinese medicine with UC prevention and treatment effects and their effects

Traditional Chinese medicine has a long history in treating UC, and its curative effect is noticeable. In particular, traditional Chinese medicine's active ingredients, such as polyphenols, alkaloids, quinones, and terpenoids, have shown therapeutic potential for UC.


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Polyphenols

Polyphenols are compounds with multiple phenolic hydroxyl groups found in many traditional Chinese medicines. Among them, resveratrol, rutin, silymarin, curcumin and other compounds have been reported to have the effect of treating UC. Resveratrol is often found in common Chinese medicines such as *Cassia*, *Veratrum*, *Polygonum cuspidatum*, etc., and plays an essential role in treating and preventing various diseases. Rauf et al.4, and Marques et al.6 found that resveratrol can treat inflammation by down-regulating inflammatory biomarkers such as TNF-α, cyclooxygenase 2, C-reactive protein, and interferon. Rutin, also known as rutin, is found in Chinese medicine such as Sophora japonica, buckwheat leaves, dandelion, etc. It is mainly used for anti-inflammatory, anti-viral, and anti-oxidants. Nones et al.1, and Habtemariam et al.8 found that rutin can inhibit TNF-α and nuclear factor kB (nuclear factor kappa-B, NF-κB). The flavonoid lignan compound silymarin extracted from milk thistle has anti-cancer and anti-inflammatory effects. Silymarin can scavenge free radicals and reactive oxygen species and reduce the release of histamine and TNF-α, IL-6, and IL-8. The expression of UC can effectively improve the inflammatory symptoms of UC.10 Curcumin is derived from the ginger family plant turmeric. It is often used as a food additive and has many functions, such as anti-inflammatory, anti-oxidant, anti-tumor, liver protection, and anti-angiogenesis. Therefore, curcumin has a good effect on the treatment of UC11.

Alkaloids

Alkaloids are a kind of basic organic compounds containing nitrogen. In recent years, the alkaloids in some Chinese medicines have shown sound UC treatment effects. Berberine, an isoquinoline alkaloid extracted from the Ranunculaceae plant Coptidis, is often used to treat bacterial-related diarrhoea. It can be used clinically for anti-inflammatory, anti-tumor and immune regulation. Studies have shown that berberine can improve UC by inhibiting the expression of certain inflammatory factors. Sinomenine is an alkaloid component extracted from the Chinese vine's roots, a fang chi family plant, and is often used to treat rheumatoid arthritis. Researchers have recently found that sinomenine also has a specific role in treating chronic inflammation. Sinomenine can reduce inflammation in UC mice induced by dextran sulfate sodium (DSS) by regulating the Nrf2/NOQ-1 signaling pathway. Oxymatrine is an active ingredient isolated from the legume Sophora flavescens. Studies have confirmed that oxymatrine has anti-hepatitis virus and anti-tumor effects. Xiong Yongai and Zhou et al.15 found that sinomenine can reduce inflammation in UC mice induced by dextran sulfate sodium (DSS) by regulating the NFκB signaling pathway. Oxymatrine is an active ingredient isolated from the legume Sophora flavescens. Studies have confirmed that oxymatrine has anti-hepatitis virus and anti-tumor effects. Xiong Yongai et al.16 conducted experiments to prove that oxymatrine clearly affects trinitrobenzene sulfonic acid (TNBS)-induced UC in SD rats. Piperine extracted from black pepper and tetrandrine extracted from tetrandrine have also been confirmed to have certain anti-UC effects.17-18

Quinones

The quinones that have the therapeutic effect of UC are mainly emodin and rhein. Emodin is an anthraquinone derivative contained in most Chinese medicines. It has anti-tumor, antibacterial, diuretic and vasodilator effects. Studies have found that emodin can treat UC by reducing the level of anti-flagellin antibodies in the blood and down-regulating the expression of Toll-like receptor 5 (TLRS) and NFκB p65 pathway.19-20. Rhein is an anthraquinone compound often used to treat gastrointestinal diseases, which can reduce the level of pro-inflammatory factors induced by lipopolysaccharide in macrophages RAW264.7.21. Studies have also found that cymodoquinone extracted from the vine fruit of centipede can also reduce the expression of inducible nitric oxide synthase (iNOS), TNF-α, IL-1β, and IL-6 to alleviate inflammation.22

Terpenes

Terpenes are the general term for isoprene polymers and their derivatives. Studies have found that certain sesquiterpenes, diterpenoids, and triterpenoids can treat UC. Tripterygium wilfordii, a pentacyclic triterpene component extracted from Tripterygium wilfordii, has potential therapeutic effects on inflammation, cancer and arthritis.23 Jia et al.24 found that tripterygium can inhibit necroptosis and relieve DSS-induced inflammation in UC mice. Parthenolide is a sesquiterpene lactone compound and an essential effective component of Asteraceae plants. It has biological activities such as anti-oxidative stress, anti-inflammatory, and inhibiting cell apoptosis. Studies have found that parthenolide can be used as an inhibitor of the NFκB pathway to relieve DSS-induced UC in mice.25 The diterpene component ester andrographolide is an important component in Andrographis paniculata, which can affect the Th1/Th2/Th17 reaction in patients with UC.26 In addition, Zhu et al.27 found that andrographolide had a good therapeutic effect on the UC mouse model induced by TNBS. The diterpenoid component dihydrostathinone has also been reported to have the potential effect of treating UC.28

Others ingredients

Other ingredients contained in traditional Chinese medicine, such as crocetin, shikimic acid, arctigenin, brucein, and polysaccharide components pectin, cellulose, chitosan, plantago seed gum, etc., have been reported to be therapeutically effective on UC.29-34. Some Chinese medicine extracts, such as ginger extract, have also been shown to have anti-inflammatory effects. Studies have found that the ingredients 6-gingerol and 6-gingerol in ginger extract can inhibit the expression of inflammation-related genes, thereby improving inflammation.35-37

Table 1 represents the active ingredients of traditional Chinese medicines that have potential effects on preventing/treating UC.

The therapeutic effect of oral colon-targeted nano-DDS in UC

Although the active ingredients of traditional Chinese medicine have the advantages of multiple pathways, multiple effective targets, and low level of adverse reactions in the treatment of UC, however, they have some shortcomings, such as strong hydrophobicity, poor permeability, and poor oral stability limit their use in the treatment of UC. To make the active ingredients of traditional Chinese medicine treat UC more effectively, some oral colon-targeting nano-systems based on particle size dependence, pH dependence, enzyme response, and active targeting have been developed. Compared with traditional oral formulations, oral colon-targeted nanoformulations have more advantages. First, it can improve the water solubility and stability of the drug, avoid damage of the intestinal environment and certain enzymes to the drug, reduce physical or chemical degradation, delay the release time of the drug, and achieve
<table>
<thead>
<tr>
<th>Chinese herbal medicine</th>
<th>UC Model</th>
<th>Animal</th>
<th>Dose</th>
<th>Mechanism</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutin</td>
<td>5% DSS</td>
<td>Male ICR mice</td>
<td>Contains 0.1% of diet</td>
<td>Inhibit the production of IL-1β, IL-6, etc., reduce oxidative stress in the colon</td>
<td>38</td>
</tr>
<tr>
<td>Quercetin</td>
<td>7.5% acetic acid solution</td>
<td>Male Swiss mice</td>
<td>10, 100 mg kg⁻¹</td>
<td>Inhibit the activity of MPO, reduce the production of pro-inflammatory factors such as IL-1β, increase the production of anti-inflammatory factors such as IL-10, scavenge free radicals, regulate the endogenous anti-oxidant glutathione, etc.</td>
<td>39</td>
</tr>
<tr>
<td>Silymarin</td>
<td>4% acetic acid</td>
<td>Male C57BL/6 mice</td>
<td>5mg kg⁻¹.d⁻¹</td>
<td>Scavenge free radicals and reactive oxygen species; reduce histamine release; reduce the expression of TNF-α, IL-6, IL-8 mRNA; block the nuclear transcription of NF-κB</td>
<td>9</td>
</tr>
<tr>
<td>Baicalein</td>
<td>TNBS</td>
<td>Female BALB/c mice</td>
<td>20mg kg⁻¹.d⁻¹</td>
<td>Inhibits inflammatory activity by targeting the caudal homeotype receptor 2/pregnane X receptor pathway; inhibits PPARγ pathway expression</td>
<td>40</td>
</tr>
<tr>
<td>Baicalin</td>
<td>2% DSS</td>
<td>Male C57BL/6 mice</td>
<td>50, 100, 150 mg kg⁻¹</td>
<td>Inhibits IL-33 expression, attenuates NF-κB expression</td>
<td>41</td>
</tr>
<tr>
<td>Icariin</td>
<td>2.5% DSS</td>
<td>Female C57BL/6 mice</td>
<td>3, 10 mg kg⁻¹</td>
<td>Inhibits expression of p65, STAT1 and STAT3 pathways</td>
<td>42</td>
</tr>
<tr>
<td>Mullein Isoflavones</td>
<td>2.5% DSS</td>
<td>Male BALB/c mice</td>
<td>25, 50 mg kg⁻¹</td>
<td>Anti-oxidant, scavenging free radicals, neuroprotective</td>
<td>43</td>
</tr>
<tr>
<td>Naringenin</td>
<td>4% acetic acid solution</td>
<td>Wistar albino rats</td>
<td>25, 50, 100 mg kg⁻¹.d⁻¹</td>
<td>Reduce lipid peroxidation and scavenge free radicals</td>
<td>44</td>
</tr>
<tr>
<td>Alpine</td>
<td>5% DSS</td>
<td>Female BALB/c mice</td>
<td>25, 50, 100 mg kg⁻¹.d⁻¹</td>
<td>Inhibits the production of pro-inflammatory factors and blocks the activation of NF-κB signaling</td>
<td>45</td>
</tr>
<tr>
<td>Curcumin</td>
<td>3% DSS</td>
<td>Male Swiss albino rat</td>
<td>100 mg kg⁻¹</td>
<td>Anti-inflammatory; anti-oxidant; anti-tumor, inhibits inflammatory pathways; scavenges free radicals; prevents mucosal damage</td>
<td>46, 47</td>
</tr>
<tr>
<td>Resveratrol</td>
<td>Enema with 7.5 mg·mL⁻¹ oxazolone solution</td>
<td>Wister albino rats</td>
<td>10 mg kg⁻¹</td>
<td>Downregulation of TNF-α, COX-2, iNOS, C-reactive protein, interferons and several interleukins</td>
<td>48</td>
</tr>
<tr>
<td>Piclitaxel</td>
<td>Enema with 50% ethanol solution of TNBS</td>
<td>Male SD rats</td>
<td>10 mg kg⁻¹</td>
<td>Regulates the activity of NF-κB, Nrf2, hypoxia-inducible factor-1</td>
<td>49</td>
</tr>
<tr>
<td>Ellagic acid</td>
<td>5% DSS acute UC, 1% DSS chronic UC</td>
<td>Female BALB/c mice, C57BL/6 mice</td>
<td>Contains 1%, 2% diet</td>
<td>Decrease IL-6, TNF-α, IFN-γ, COX-2 and iNOS activity; down</td>
<td>50</td>
</tr>
<tr>
<td>Magnolol</td>
<td>5% DSS</td>
<td>C57BL/6 mice</td>
<td>25, 50, 100 mg kg⁻¹</td>
<td>Regulate signaling pathways p38MAPK, NF-κB, block STAT3 pathway Inhibit TNF-α, IL-1β, IL-12 by regulating NF-κB and PPARγ pathways</td>
<td>51</td>
</tr>
</tbody>
</table>

Table 1. Representative active components of Chinese medicine with prevention and treatment effect of UC and its mechanisms.
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<table>
<thead>
<tr>
<th>Component</th>
<th>Formulation</th>
<th>Mice/Species</th>
<th>Dose</th>
<th>Effect/Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berberine</td>
<td>5% DSS</td>
<td>Male Wistar rats</td>
<td>10, 30, 50 mg kg⁻¹</td>
<td>Activates AMPK enzymes, inhibits the expression of IL-1, IL-1β, IL-6, IL-12, TNF-α, TGF-β and IFN-γ, upregulates the expression of IL-4 and IL-10; increases the expression of SfGa, decreased the expression of iNOS, MPO and malondialdehyde</td>
</tr>
<tr>
<td>Tetrandrine</td>
<td>5% DSS</td>
<td>Female BALB/c mice</td>
<td>40 mg kg⁻¹ d⁻¹</td>
<td>Anti-inflammatory, inhibit the activation of NF-κB pathway</td>
</tr>
<tr>
<td>Sinomenine</td>
<td>3% DSS</td>
<td>Female C57BL/6 mice</td>
<td>100 mg kg⁻¹</td>
<td>Reduce TNF-α, IL-6, iNOS, SOD levels; activate Nrf2 and its downstream genes, heme oxidase-1 and NADP(H)quinone oxidoreductase-1</td>
</tr>
<tr>
<td>Piperine</td>
<td>5% DSS</td>
<td>Male BALB/c mice</td>
<td>2 mg kg⁻¹</td>
<td>Inhibits the activity of metabolic enzymes, regulates the release of p-glycoprotein efflux pump and NF-κB, and provides protection against oxidative damage sites</td>
</tr>
<tr>
<td>Emodin</td>
<td>3% DSS</td>
<td>Male C57BL/6 mice</td>
<td>5, 10, 20 mg kg⁻¹</td>
<td>Decreases the level of anti-flagellin antibodies in sepsis and reduces the expression of TLR5 and NF-κBp65</td>
</tr>
<tr>
<td>Rhein</td>
<td>Tail docking-induced inflammation</td>
<td>Transgenic Zebrafish</td>
<td>1, 2, 20 μg mL⁻¹</td>
<td>Decrease the activity of MPO in the colonic mucosa and reduce diarrhea due to ulcers</td>
</tr>
<tr>
<td>Quinone</td>
<td>3% aqueous acetic acid enema</td>
<td>Male Wistar rats</td>
<td>25, 50 mg kg⁻¹</td>
<td>Has anti-inflammatory, analgesic, anti-oxidant, and healing-promoting effects; inhibits NF-κB signaling pathway</td>
</tr>
<tr>
<td>Triptolide</td>
<td>5% DSS</td>
<td>Female C57BL/6 mice</td>
<td>1 mg kg⁻¹</td>
<td>Has immunomodulatory, anti-inflammatory and anti-tumor activities; inhibits RIP3/MLKL apoptosis pathway</td>
</tr>
<tr>
<td>Parthenolide</td>
<td>5% DSS</td>
<td>Male BALB/c mice</td>
<td>10 mg kg⁻¹</td>
<td>Inhibit the activation of NF-κB pathway and inhibit the expression of pro-inflammatory factors</td>
</tr>
<tr>
<td>Dihydrorotauhinone</td>
<td>5% DSS</td>
<td>Male C57BL/6 mice</td>
<td>10, 25 mg kg⁻¹</td>
<td>Inhibits MPO activity; reduces levels of inflammatory factors TNF-α, IL-1β, IL-6 and high mobility group box protein</td>
</tr>
<tr>
<td>Andrographolide</td>
<td>2.5% TNBS, enema</td>
<td>C57BL/6 mice</td>
<td>0.1 g kg⁻¹ d⁻¹</td>
<td>Reduce blood levels of pro-inflammatory factors TNF-α, IL-1β, IL-6 and IL-17A, and reduce levels of IFN-γ</td>
</tr>
<tr>
<td>Shikimic acid</td>
<td>2.5% TNBS, enema</td>
<td>Male BALB/c mice</td>
<td>200 mg kg⁻¹</td>
<td>Anti-inflammatory, affects the metabolism of arachidonic acid, inhibits platelet aggregation, inhibits arterial and venous thrombosis</td>
</tr>
<tr>
<td>Arctigenin</td>
<td>DSS</td>
<td>Male BALB/c mice</td>
<td>25, 50 mg kg⁻¹</td>
<td>Inhibit the expression of several genes related to inflammation in the colon such as TNF-α, IL-6, macrophage inflammatory protein 2, monocyte chemotactic protein 1, immunoglobulin adhesion molecule 1 and vascular adhesion factor 1</td>
</tr>
</tbody>
</table>
the purpose of sustained release; second, when the drug is prepared for oral administration in colon-targeting nanoformulations, nano-level particles have better targeting in the colon and can effectively alleviate system adverse reactions. Finally, due to the small particle size of the nano-preparation, the drug is more likely to accumulate in the inflammation site of the colon, and a lower drug concentration can achieve a good therapeutic effect.

**Particle size-dependent type**

Studies have shown that the intestinal mucosal layer in the affected area of UC is destroyed, inflammation-related cells such as macrophages increase, destroying the original intestinal environment. Macrophages can preferentially absorb nano-scale particles. At the same time, active drugs can be delivered to colon inflammatory tissues through colonic epithelial high permeability and retention effect (enhanced permeability and retention effect, EPR) effects. Lamprecht et al. prepared 3 kinds of nanoparticles with fluorescent pigments (with a particle size of 0.1, 1, and 10 μm, respectively), and observed the distribution of various particles after 3 days in UC rats induced by TNBS. The distribution index of the sizes of the nanoparticles in the colon is (5.2 ± 3.8), (9.1 ± 4.2) and (14.5 ± 6.3), respectively. Therefore, in the diseased area of UC, when the particle size is small enough, the drug particles can penetrate into the cell, thereby promoting its rapid passage through the mucosal barrier, interacting with the immune system, and improving the uptake, absorption, distribution and metabolism of the drug.

Ma et al. used the emulsification solvent evaporation method to prepare curcumin-loaded particles (with a particle size of 1.7 μm) and nanoparticles (with a particle size of 270 nm). Compared with the particles, the nanoparticles have a higher release rate; Curcumin nanoparticles are easier to alleviate DSS-induced UC inflammation in mice.

**pH-dependent**

The pH of the gastrointestinal tract gradually rises from the stomach to the colon. According to the characteristics of colon pH 7-8, a pH-dependent nano-delivery system can be designed, and the nano-system can be targeted for release in the colon. A pH-dependent drug delivery system can be designed by wrapping pH-sensitive biodegradable polymer materials on the surface of the drug. Methacrylic acid polymer Eudragit® is a common pH-sensitive material. It can be dissolved in different pH by changing its side chain. Raj et al. prepared a pH-sensitive curcumin nanoformulation, first prepared a chitosan-encapsulated nano-core structure by the particle gel method, and then prepared the Eudragit FS 30D shell by the emulsification solvent evaporation method to obtain the core-shell structure. This nanoparticle has the ability of controlled release of drugs and colon targeting. In the release experiment, the cumulative release rate of chitosan nanoparticles coated with pH-sensitive materials in the simulated colon fluid (pH 7.4) reached 84.7%, and the drug was continuously released within 24 hours. Beloqui et al. also dissolved curcumin, pH sensitive Eudragit® S100, poly (lactic-co-glycolic acid) [PLGA] in the organic phase and then dropped it into the organic phase. The pH-sensitive nano-preparation was prepared by stirring in the aqueous solution. The nano-preparation system hardly released curcumin in the pH 1.5 gastric simulation solution and pH 4.5 small intestine simulation solution, and the curcumin release rate after 1 h in the pH 7.2 colon simulation solution reached 90%. In cell uptake experiments, curcumin nanoparticles can penetrate the epithelial barrier more easily than curcumin free solution, and increase the absorption of curcumin by colon cancer Caco-2 cells. In in vivo experiments, pH-sensitive curcumin nanoparticle preparations significantly reduced DSS-induced infiltration of mouse neutrophils and TNF-α secretion, lowered the level of MPO, alleviated DSS-induced body weight decline in mice, and inhibited colon shortening; In HE staining, the pH-sensitive nano-preparation group significantly alleviated the inflammation in the colon. Rutin, ellagic acid, sinomenine, etc. have also been reported to have pH-sensitive nanoformulations for the treatment of UC.

**Enzyme-responsive**

Studies have shown that the colon contains a large number of beneficial microorganisms, which can produce highly active proteases and peptide enzymes, which can be used to make colon enzyme-sensitive nano preparations. After the preparation reaches the colon, the enzyme-sensitive material degrades to release the drug, which improves the bioavailability of the drug. Castanga et al. used the ultrasonic reaction method to prepare enzyme-sensitive quercetin liposomes to treat UC. Nutriose is a soluble maize dextrin that uses Nutriose’s enzymatic degradability to prepare enzyme-sensitive composite liposomes. In vivo distribution experiments showed that the liposomes without
<table>
<thead>
<tr>
<th>Name</th>
<th>Carrier</th>
<th>Preparation</th>
<th>Delivery principle</th>
<th>Formulation characteristics</th>
<th>Therapeutic effect on UC</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLGA, ABC</td>
<td></td>
<td>Double emulsification solvent evaporation</td>
<td>Porous Nano</td>
<td>The cumulative release at 96 h is about 76%, which is 58% higher than that of nonporous PLGA-encapsulated nanoparticles (58%).</td>
<td>Significantly higher UC microbody weight, colon length; spleen body mass ratio; inflammatory response; Fecal Lcn-2, MPO levels; CD98 and TNF-α expression levels.</td>
<td>78</td>
</tr>
<tr>
<td>PLGA, HA, CS</td>
<td></td>
<td>Double Emulsion Solvent Evaporation Technology</td>
<td>Active targeting</td>
<td>The cumulative release of siCD98 and CUR at 72 h was 68.8% and 89.7%, respectively; increased Colon-26 cells</td>
<td>MPO, spleen mass; IL-6, IL-10, TNF-α expression levels; IL-10 expression levels.</td>
<td>74</td>
</tr>
<tr>
<td>PLGA, PF127, ABC</td>
<td></td>
<td>Improved double emulsification solvent evaporation technology</td>
<td>Porous Nano</td>
<td>The cumulative release rate at 48 h was 58.3%; there was more accumulation in colon tissue</td>
<td>MPO, DA11; TNF-α1, IL-107</td>
<td>76</td>
</tr>
<tr>
<td>SF, CS</td>
<td></td>
<td>Solvent-free self-assembly</td>
<td>Active targeting</td>
<td>Enhanced cellular uptake of Raw264.7</td>
<td>MPO, DA11; TNF-α, IL-107</td>
<td>72</td>
</tr>
<tr>
<td>Endragnet® S100,</td>
<td></td>
<td>Improved spontaneous emulsification solvent dispersion method</td>
<td>pH-dependent</td>
<td>Curcumin does not release at pH 1.5, 4.5, but is rapidly released at neutral pH 7.2</td>
<td>MPO1; TNF-α protein expression in blank nano group; In tissue staining, inflammatory reaction; Body mass; MPO1; Spleen mass; colon length; In HE staining, inflammatory response.</td>
<td>11</td>
</tr>
<tr>
<td>Eudyne® S100, PLGA</td>
<td></td>
<td>Emulsifying solvent evaporation method</td>
<td>pH-dependent</td>
<td>There is no burst release in the release test, more curcumin can be released in neutral pH, and the release can be controlled.</td>
<td>MPO1; TNF-α protein expression in blank nano group; In tissue staining, inflammatory reaction; Body mass; MPO1; Spleen mass; colon length; In HE staining, inflammatory response.</td>
<td>79</td>
</tr>
<tr>
<td>HS-15, PG</td>
<td></td>
<td>Self-assembly nano-emulsification method</td>
<td>Other</td>
<td>The optimized particle size is (18.0±0.59) nm and the potential is (−15.7±0.42) mV</td>
<td>DA11; IL-10, TGF-β and other anti-inflammatory factors; IL-1β, IL-6, IL-8 and other pro-inflammatory factors; iNOS, COX-2 mRNA expression levels; TLR4, MyD88, TRAF6, NF-κBp65</td>
<td>77</td>
</tr>
<tr>
<td>Hesperitin</td>
<td></td>
<td>Eudyne® 530D Eudyne® RLP1</td>
<td>pH-dependent</td>
<td>The cumulative release rate after 24 h in simulated colonic fluid (pH 7.2) was (40.8±5.5%)</td>
<td>Mucosal injury; MPO, IL-6, TNF-α1</td>
<td>80</td>
</tr>
<tr>
<td>Nutriose FM06</td>
<td></td>
<td>Ultrasonic reaction method</td>
<td>Enzyme sensitive</td>
<td>About 20% of quercetin was detected in the jejunum and ileum and about 30% in the colon 3 hours after dosing</td>
<td>Reduced colonic body mass ratio more than unencapsulated Nutriose formulation; MPO2; MPO 1 percentage.</td>
<td>70</td>
</tr>
<tr>
<td>Quercetin</td>
<td>CS</td>
<td>Internal Emulsion Gel Technology</td>
<td>Enzyme sensitive</td>
<td>The cumulative release rate was 10% in simulated gastric and small intestinal fluid, and 65.6% in simulated colonic fluid</td>
<td>Colonic mucosa PGE2; TNF-α1; iNOS, COX-2 71 mRNA levels.</td>
<td>71</td>
</tr>
<tr>
<td>Icariin</td>
<td></td>
<td>Endragnet® CS</td>
<td>Other</td>
<td>The release rate was (8.91±0.39) % at pH 6.8, (59.5±2.13) % at pH 7.4, and (72.5±1.33) % in simulated colonic fluid</td>
<td>DA11; expression levels of MyD88, NF-κBp65; TLR/NF-κB pathway; IFN-γ, IL-1β and other pro-inflammatory factors.</td>
<td>66</td>
</tr>
<tr>
<td>Sinomenine</td>
<td>CS</td>
<td>Emulsification Crosslinking and Emulsification Solvent Evaporation</td>
<td>Other</td>
<td>The optimized nanoemulsion droplet size is (122±11) nm</td>
<td>Ucker index; tissue damage score; small intestinal mucosal damage.</td>
<td>81</td>
</tr>
<tr>
<td>Antilogerine</td>
<td>VCO</td>
<td>High pressure homogenization self-emulsifying method</td>
<td>Other</td>
<td>The particle size ranges from (196±3.57) to (269±1.05) nm, the potential ranges from −56.6 to −62.0 mV</td>
<td>CAS1; colonic mucosal edema, necrosis and inflammatory cell infiltration; promote MPO, I.P, GSH, LDH back to normal levels.</td>
<td>82</td>
</tr>
</tbody>
</table>

Table 2. Colon-targeted nano drug delivery systems of active components of Chinese medicine in the treatment of UC.
Nutriose Ig 4 h showed strong fluorescence in the ileum and cecum, but only weak fluorescence in the colon; the liposomes without Nutriose Ig 4 h showed obvious fluorescence in the colon. In addition, the nano-delivery system can delay drug release. In the release experiment, the cumulative release rate of Nutriose-encapsulated liposomes in the colon simulant at pH 7.0 for 8 hours is 15% lower than that of unencapsulated liposomes. In the in vivo efficacy experiment, the nano-preparation group significantly reduced bleeding and ulcers in the colon area, lowered the colonic edema tissue (CAS) index, and decreased the activity of MPO. Chitosan-coated calcium alginate microspheres loaded with icariin can also target drug delivery to the colon through an enzyme response.

**Active targeting**

Studies have found that there are a large number of inflammation-related proteins in the inflammation part of the colon. When a substance that can specifically bind to the nanoparticle is connected, colon targeting can be achieved through the ligand-receptor effect. Chondroitin sulfate (CS) is a glycosaminoglycan substance that binds to the CD44 receptor. CD44 is a transmembrane transport glycoprotein on the surface of activated macrophages. Gou et al. used silk fibroin to prepare curcumin nanoparticles and then attached CS to their surface to target colonic macrophages. In the macrophage uptake experiment, the fluorescence of chondroitin sulfate nanoparticles (CS-NPS) was significantly stronger than that of curcumin nanoparticles after 4 hours of treatment. After CS-NPS Ig, it significantly inhibited mice's body weight decline, down-regulated TNF-α and IL-6, and upregulated the levels of IL-10; in the HE staining experiment, the accumulation of immune cells was reduced. After CS-NPS Ig, the survival rate of mice after 15 d DSS treatment reached 50%. Studies have found that the up-regulation of CD98 in colonic epithelial cells in mice with colon inflammation can be used to treat UC by interfering with its synthesis. Xiao et al. prepared curcumin hydrogels containing CD98 synthetic interfering RNA (CD98 siRNA, siCD98) for targeted treatment of UC. Use PLGA to wrap curcumin and siCD98 to form nanoparticles, then wrap chitosan and connect with hyaluronic acid, and finally crosslink into a hydrogel in the presence of chitosan and sodium alginate. In the cell uptake experiment, the fluorescence of the hyaluronic acid nanoparticle group was more potent than that of the curcumin nanoparticle group, which proved that the surface modification of hyaluronic acid (HA) could increase the cell's uptake of nanoparticles. Further cell experiments showed that the nano-preparation system reduces the expression of CD98 in Colon-26 colon cancer cells, down-regulating the levels of MPO and apolipoprotein 2 (Lcn-2) in feces, reduces colon ulcers, and promotes colon tissue returns to normal. Some researchers have also loaded targeted siRNA into ginger-derived natural nanoparticles for targeted therapy of UC.

**Other ingredients**

In addition to the targeted nano-systems mentioned above, there are also some porous nanof ormulations and self-assembled nano-delivery systems for colon-targeted delivery of active ingredients of traditional Chinese medicine. Chen et al. used dual emulsification solvent eva-
poration technology to use PLGA/PF127 to encapsulate curcumin and ammonium bicarbonate (ABC) as a porogen to produce porous nanoparticles. In macrophage uptake experiments, porous nanoparticles, the fluorescence of the preparation is stronger than that of the non-porous nanoparticle preparation. In vivo experiments show that porous nanoparticles have more accumulation in colon tissue. Dou et al.23 constructed bruceine nanoparticles by self-assembly nano-emulsification method and dissolved bruceine D (BD) in (polyethylene glycol-15-hydroxystearate)-propylene glycol. In the chain triacylglycerol (4:2:1) solution, the self-assembled nanoparticles can be obtained by stirring. Compared with BD-free solution, BD self-assembled nano-system has a better inhibitory effect on pro-inflammatory factors and can significantly alleviate the damage of UC tissue.

The delivery principle of the oral colon-targeted nano-system is shown in Figure 1, and the oral colon-targeted nano-system for treating UC with active ingredients of traditional Chinese medicine is shown in Table 2.

Conclusions

Traditional Chinese medicine has the characteristics of multiple components and multiple targets and has significant advantages in treating chronic and complex diseases represented by UC. With the deepening of research, the effective ingredients of traditional Chinese medicine intervention in UC have been discovered. The mechanism has gradually become clear, such as curcumin, triptolide, resveratrol, etc. However, in the formulation development process, problems such as water insolubility, low bioavailability, and poor colon targeting have restricted its use. Therefore, how to effectively deliver drugs to the diseased part of the colon through oral administration to release the drugs to achieve the therapeutic effect is a problem to be solved urgently. The construction of an oral colon-targeted drug delivery system can solve this problem. Nanoformulations for treating UC can be designed according to particle size dependence, pH dependence, enzyme response, and ligand-receptor-specific pairing. Some nanoformulations pass through the colon. The permeability of mucosal cells is not high, and there are problems such as inflammation or low uptake of immune-related cells. These problems will further limit the use of colon-targeted nanoformulations in clinical applications. However, in recent years, with the application of new materials, the discovery of colon-specific receptors, and the research on the pathogenesis of UC, the colon targeting and specificity of oral preparations will be further improved.

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Conflicts of Interest

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Bibliographic references


