REVIEW / ARTÍCULO DE REVISIÓN

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

Mohammad Javed Ansari[1]*, Suhad J. Hadi[2], Hamzah H. Kzar[2], Moaed E. Al-Gazally[3], Thulfeqar Ahmed Hamza[4], Mohammed Khudair Hasan[5], Aiman Mohammed Baqir Al-Dhalimy[6], Reza Akhavan-Sigari[7,8]
DOI. 10.21931/RB/2023.08.02.17

[1] Department of Pharmaceutics, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-kharj, Saudi Arabia.
[2] Veterinary Medicine Collage, Al-Qasim Green University, Al-Qasim, Iraq.
[3] College of Medicine, University of Al-Ameed, Karbala, Iraq.
[4] Medical Laboratory Techniques Department, Al-Mustaqbal University College, Babylon, Iraq.
[5] Al-Manara College of Medical sciences, Department of Pharmacy, Missan, Iraq.
[6] College of Nursing, Altoosi University College, Najaf, Iraq and The Islamic University, Najaf, Iraq.
[7] Department of Neurosurgery, University Medical Center Tuebingen, Germany.
[8] Department 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 area[1]. 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 factors[2]. 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 medicine[3]. 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.

Citation: Oral Nano-Delivery Systems for Colon-Targeted Drug Delivery of Traditional Chinese Medicine in Ulcerative Colitis. Ansari M J, Hadi S J,. Kzar H H,Al-Gazally M E, Ahmed HamzaT, Khudair Hasan M, Baqir Al-Dhalimy A M, Akhavan□Sigari R. Revis Bionatura 2023;8 (2) 17. http://dx.doi.org/10.21931/RB/2023.08.02.17
Received: 2 January 2023 / **Accepted:** 19 April 2023 / **Published:** 15 June 2023
Publisher's Note: Bionatura stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

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.*[5] 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[6]. Nones *et al.*[7], and Habtemariam *et al.*[8] found that rutin can inhibit TNF-α and nuclear factor κB (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[9,10]. 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 UC[11].

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 diarrhea.

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[12]. 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[13]. Tang *et al.*[14] and Zhou *et al.*[15] found that sinomenine can reduce inflammation in UC mice induced by dextran sulfate sodium (DSS) by regulating the Nrf2/NQO-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 *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 has 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 (TLR5) and NF-κB 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 cylindroquinone 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

Terpenoids 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 NF-κB 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 dihydrotanshinone 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 therapeutic effect 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

Chinese herbal medicine		UC Model	Animal	Dose	Mechanism	Ref
Group	Name					
Polyphenols	**Rutin**	5% DSS	Male ICR mice	Contains 0.1% of diet	Inhibit the production of IL-1β, IL-6, etc., reduce oxidative stress in the colon	38
	Quercetin	7.5% acetic acid solution	Male Swiss mice	10, 100 $mg \cdot kg^{-1}$	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.	39
	Silymarin	4% acetic acid	Male C57BL/6 mice	$5mg \cdot kg^{-1} \cdot d^{-1}$	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	9
	Baicalein	TNBS	Female BALB/c mice	$20mg \cdot kg^{-1} \cdot d^{-1}$	Inhibits inflammatory activity by targeting the caudal homeotype receptor 2/pregnane X receptor pathway; inhibits PPARγ pathway expression	40
	Baicalin	2% DSS	Male C57BL/6 mice	50, 100, 150 $mg \cdot kg^{-1}$	Inhibits IL-33 expression, attenuates NF-κB expression	41
	Icariin	2.5% DSS	Female C57BL/6 mice	3, 10 $mg \cdot kg^{-1}$	Inhibits expression of p65, STAT1 and STAT3 pathways	42
	Mullein Isoflavones	2.5% DSS	Male BALB/c mice	25, 50 $mg \cdot kg^{-1}$	Anti-oxidant, scavenging free radicals, neuroprotective	43
	Naringenin	4% acetic acid solution	Wister albino rats	25, 50, 100 $mg \cdot kg^{-1} \cdot d^{-1}$	Reduce lipid peroxidation and scavenge free radicals	44
	Alpine	5% DSS	Female BALB/c mice	25, 50, 100 $mg \cdot kg^{-1} \cdot d^{-1}$	Inhibits the production of pro-inflammatory factors and blocks the activation of NF-κB signaling	45
	Curcumin	3% DSS	Male Swiss albino rat	100 $mg \cdot kg^{-1}$	Anti-inflammatory, anti-oxidant, anti-tumor, inhibits inflammatory pathways; scavenges free radicals; prevents mucosal damage	46, 47
	Resveratrol	Enema with 7.5 mg·mL−1 oxazolone solution	Wister albino rats	10 $mg \cdot kg^{-1}$	Downregulation of TNF-α, COX-2, iNOS, C-reactive protein, interferons and several interleukins	48
	Picclitaxel	Enema with 50% ethanol solution of TNBS	Male SD rats	10 $mg \cdot kg^{-1}$	Regulates the activity of NF-κB, Nrf2, hypoxia-inducible factor-1	49
	Ellagic acid	5% DSS acute UC; 1% DSS chronic UC	Female BALB/c mice; C57BL/6 mice	Contains 1%, 2% diet	Decrease IL-6, TNF-α, IFN-γ, COX-2 and iNOS activity; down	50
	Magnolol	5% DSS	C57BL/6 mice	25, 50, 100 $mg \cdot kg^{-1}$	Regulate signaling pathways p38MAPK, NF-κB, block STAT3 pathway Inhibit TNF-α, IL-1β, IL-12 by regulating NF-κB and PPARγ pathways	51

Table 1. Representative active components of Chinese medicine with prevention and treatment effect of UC and its mechanisms.

Alkaloid	**Berberine**	5% DSS	Male Wistar rats	10, 30, 50 $mg \cdot kg^{-1}$	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 SIgA , decreased the expression of iNOS, MPO and malondialdehyde	12
	Tetrandrine	5% DSS	Female BALB/c mice	40 $mg \cdot kg^{-1} \cdot d^{-1}$	Anti-inflammatory, inhibit the activation of NF-κB pathway	18
	Sinomenine	3% DSS	Female C57BL/6 mice	100 $mg \cdot kg^{-1}$	Reduce TNF-α, IL-6, iNOS, SOD levels; activate Nrf2 and its downstream genes, heme oxidase-1 and NADP(H)quinone oxidoreductase-1	14, 15
	Piperine	5% DSS	Male BALB/c mice	2 $mg \cdot kg^{-1}$	Inhibits the activity of metabolic enzymes, regulates the release of p-glycoprotein efflux pump and NF-κB, and provides protection against oxidative damage sites	17
Quinones	**Emodin**	3% DSS	Male C57BL/6 mice	5, 10, 20 $mg \cdot kg^{-1}$	Decreases the level of anti-flagellin antibodies in serum and reduces the expression of TLR5 and NF-κBp65	20
	Rhein	Tail docking-induced inflammation	Transgenic Zebrafish	1, 2, 20 $\mu g \cdot mL^{-1}$	Decrease the activity of MPO in the colonic mucosa and reduce diarrhea due to ulcers	21
	Quinone	3% aqueous acetic acid enema	Male Wistar rats	25, 50 $mg \cdot kg^{-1}$	Has anti-inflammatory, analgesic, anti-oxidant, and healing-promoting effects; inhibits NF-κB signaling pathway	22
Terpenes	**Triptolide**	5% DSS	Female C57BL/6 mice	1 $mg \cdot kg^{-1}$	Has immunomodulatory, anti-inflammatory and anti-tumor activities; inhibits RIP3/MLKL apoptosis pathway	24, 52
	Parthenolide	5% DSS	Male BALB/c mice	10 $mg \cdot kg^{-1}$	Inhibit the activation of NF-κB pathway and inhibit the expression of pro-inflammatory factors	25
	Dihydrotanshinone	5% DSS	Male C57BL/6 mice	10, 25 $mg \cdot kg^{-1}$	Inhibits MPO activity; reduces levels of inflammatory factors TNF-α, IL-1β, IL-6 and high mobility group box protein	28
	Andrographolide	2.5% TNBS, enema	C57BL/6 mice	0.1 $g \cdot kg^{-1} \cdot d^{-1}$	Reduce blood levels of pro-inflammatory factors TNF-α, IL-1β, IL-6 and IL-17A, and reduce levels of IFN-γ	27
Others	**Shikimic acid**	2.5% TNBS, enema	Male BALB/c mice	200 $mg \cdot kg^{-1}$	Anti-inflammatory, affects the metabolism of arachidonic acid, inhibits platelet aggregation, inhibits arterial and venous thrombosis	1, 33
	Arctigenin	DSS	Male BALB/c mice	25, 50 $mg \cdot kg^{-1}$	Inhibit the expression of several genes related to inflammation in the colon such as TNF-α, IL-6, macrophage inflammatory protein 2, monocyte chemoattractant protein 1, immunoglobulin adhesion molecule 1 and vascular adhesion factor 1	32

Table 1. Representative active components of Chinese medicine with prevention and treatment effect of UC and its mechanisms.

	Crocus acid	TNBS/ethanol, enema	SD rats	25, 50 $mg \cdot kg^{-1}$	Inhibit NF-κB inflammatory pathway	29
	Brucein	3% DSS	Male BALB/c mice	0.5, 1, 2 $g \cdot kg^{-1}$	Regulation of TLR4-linked NF-κB signaling	34

MPO-myeloperoxidase PPARγ-peroxisome proliferator-activated receptor γ STAT-signal transducer and activator of transcription
COX-2- cyclooxygenase 2 IFN-γ-interferon γ TGF-β-transforming growth factor β Nrf2-nuelear factor E2-related factor 2

Table 1. Representative active components of Chinese medicine with prevention and treatment effect of UC and its mechanisms.

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[53-54]. 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[55].

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[56]. Lamprecht *et al.*[58] 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 ig 3 d in UC rats induced by TNBS. The distribution index of the size 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[58,59]. Ma *et al.*[60] 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[54,61,62]. 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.*[63] 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 the 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.*[11] also dissolved curcumin, pH sensitizer 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[64], ellagic acid[65], sinomenine[66], 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[67-69]. Castangia *et al.*[70] 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

Name	Carrier	Preparation	Delivery principle	Formulation characteristics	Therapeutic effect on UC	Ref
Curcumin	PLGA, ABC	Double emulsification solvent evaporation	Porous Nano	The cumulative release at 96 h is about 76%, which is 58% higher than that of nonporous PLGA-encapsulated nanoparticles (58%).	Significantly higher UC mice body weight, colon length↓; spleen body mass ratio↓; inflammatory response↓	78
	PLGA, HA, CS	Double Emulsion Solvent Evaporation Technology	Active targeting	The cumulative release of siCD98 and CUR at 72 h was 68.8% and 89.7%, respectively; increased Colon-26 cells	Fecal Lcn-2, MPO levels↓; CD98 and TNF-α expression levels↓	74
	PLGA, PF127, ABC	Improved double emulsification solvent evaporation technology	Porous Nano	The cumulative release rate at 48 h was 58.3%; there was more accumulation in colon tissue	MPO, spleen mass↓; IL-6, IL-12, TNF-α expression levels↓; IL-10 expression levels↑	76
	SF, CS	Solvent-free self-assembly	Active targeting	Enhanced cellular uptake of Raw264.7	MPO, DAI↓; TNF-α↓, IL-10↑	72
	Eudragit® S100, PLGA	Improved spontaneous emulsification solvent dispersion method	pH-dependent	Curcumin does not release at pH 1.5, 4.5, but is rapidly released at neutral pH 7.2	MPO↓; TNF-α protein expression in blank nano group↓; In tissue staining, inflammatory reaction↓	11
	Eudragit® S100, PLGA	Emulsifying solvent evaporation method	pH-dependent	There is no burst release in the release test, more curcumin can be released in neutral pH, and the release can be controlled	Body mass↓; MPO↓; Spleen mass↑, colon length↓; In HE staining, inflammatory response↓	79
Brucein	HS-15、PG	Self-assembly nano-emulsification method	Other	The optimized particle size is (18.03±0.59) nm and the potential is (−15.76±0.42) mV	DAI↓; 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	77
Silymarin	Eudragit® FS30D Eudragit® RLPO	Emulsifying solvent evaporation method	pH-dependent	The cumulative release rate after 24 h in simulated colonic fluid (pH 7.2) was (40.8±5.5%)	Mucosal injury↓; MPO, IL-6, TNF-α↓	80
Quercetin	Nutriose FM06	Ultrasonic reaction method	Enzyme sensitive	About 20% of quercetin was detected in the jejunum and ileum and about 30% in the colon 3 hours after dosing	Reduced colonic body mass ratio more than unencapsulated Nutriose formulation; MPO↓; MPO I percentage↑↑	70
Icariin	CS	Internal Emulsion Gel Technology	Enzyme sensitive	The cumulative release rate was 10% in simulated gastric and small intestinal fluid, and 65.6% in simulated colonic fluid	Colonic mucosa PGE2↓; TNF-α↓; iNOS, COX-2 71 mRNA levels↓	71
Sinomenine	Eudragit®, CS	Emulsification Crosslinking and Emulsification Solvent Evaporation	Other	The release rate was (8.91±0.39) % at pH 6.8, (59.52±1.23) % at pH 7.4, and (72.54±1.33) % in simulated colonic fluid	DAI↓; expression levels of MyD88, NF-κBp65↓; TLR/NF-κB pathway↓; IFN-γ, IL-1β and other pro-inflammatory factors↓	66
Andrographolide	α-tocopherol	High pressure homogenization self-emulsifying method	Other	The optimized nanoemulsion droplet size is (122±11) nm	Ulcer index↓; tissue damage score↓; small intestinal mucosal damage	81
Quinone	SBO/VCO	Ultrasound after homogenization		The particle size ranges from (196.1±3.57) to (269.2±1.05) nm; the potential ranges from −36.6 to −62.0 mV	CAS↓; colonic mucosal edema, necrosis and inflammatory cell infiltration↓; promote MPO, LPO, GSH, LDH back to normal levels	82

Table 2. Colon-targeted nano drug delivery systems of active components of Chinese medicine in the treatment of UC.

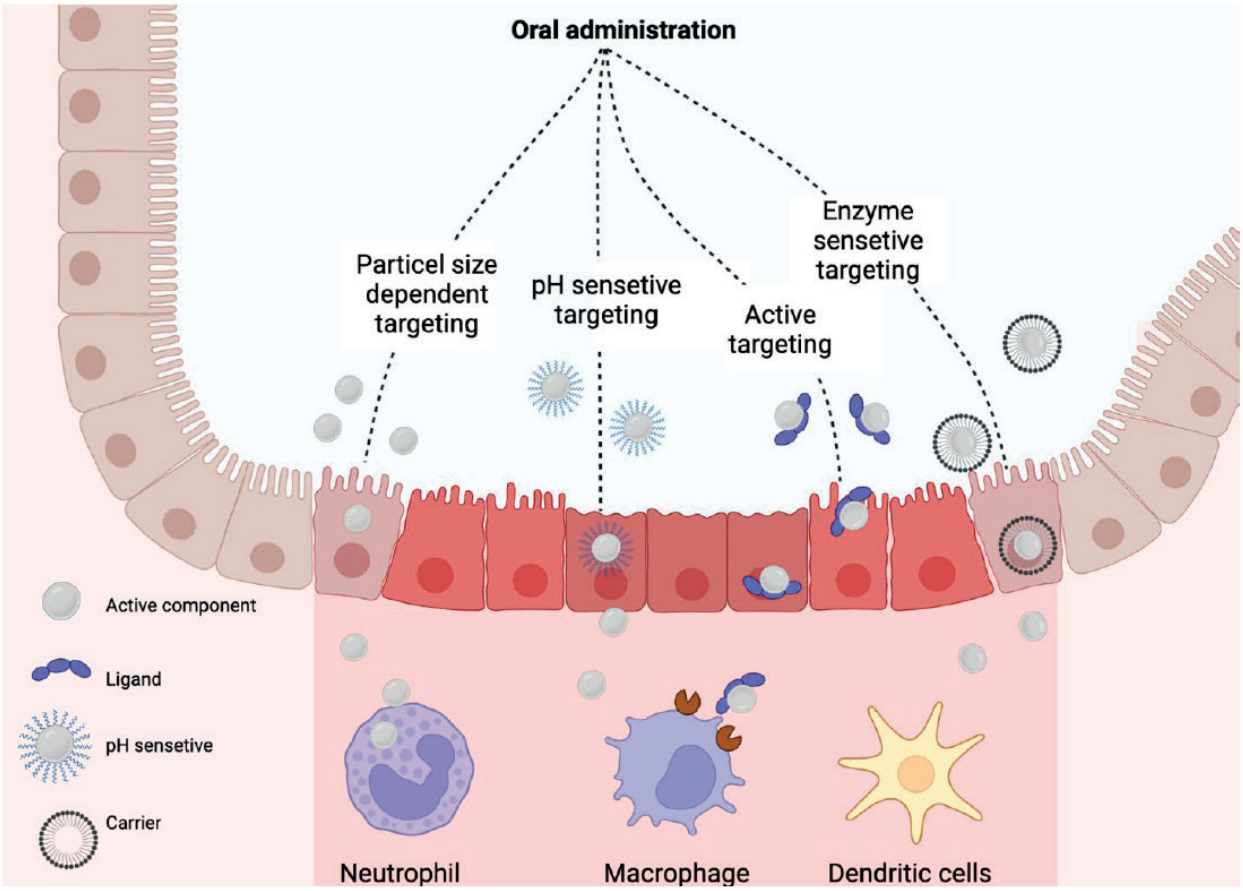

Figure 1. Delivery principles of colon-targeted nano drug delivery systems for UC.

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[71].

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.*[72] 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[73]. Xiao *et al.*[74] 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[75].

Other ingredients

In addition to the targeted nano-systems mentioned above, there are also some porous nanoformulations and self-assembled nano-delivery systems for colon-targeted delivery of active ingredients of traditional Chinese medicine. Chen *et al.*[76] 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.*[77] 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.

Author Contributions

Conceptualization and writing original draft preparation: Mohammad Javed Ansari. Methodology: Suhad J. Hadi and Hamzah H. Kzar. Validation: Moaed E. Al-Gazally. Resource: Thulfeqar Ahmed Hamza. Data collection: Mohammed Khudair Hasan. Data analysis: Aiman Mohammed Baqir Al-Dhalimy, Writing review editing: Reza Akhavan-Sigari.

Funding

This research received no external funding.

Acknowledgments

There is no acknowledgments.

Conflicts of Interest

There are no conflicts of interest.

Bibliographic references

1. Forootan M, Darvishi M. Solitary rectal ulcer syndrome: A systematic review. Medicine (Baltimore). 2018;97(18):e0565.
2. Xavier RJ, Thomas HJ. Gastrointestinal Diseases. Hunter's Tropical Medicine and Emerging Infectious Disease. 2013:18–27.
3. Chen, Y., Wang, P., Zhang, Y. et al. Comparison of effects of aminosalicylic acid, glucocorticoids and immunosuppressive agents on the expression of multidrug-resistant genes in ulcerative colitis. Sci Rep 2022;12:20656.
4. Rauf A, Imran M, Suleria H A R, et al. A comprehensive review of the health perspectives of resveratrol. Food Funct, 2017, 8(12): 4284-4305.
5. Marques F Z, Markus M A, Morris B J. Resveratrol: Cellular actions of a potent natural chemical that confers diverse health benefits. Int J Biochem Cell Biol, 2009, 41(11): 2125-2128.
6. Chua L S. A review on plant-based rutin extraction methods and its pharmacological activities. J Ethnopharmacol, 2013, 150(3): 805-817.
7. Nones K, Dommels Y E, Martell S, et al. The effects of dietary curcumin and rutin on colonic inflammation and gene expression in multidrug resistance gene-deficient (mdr1a-/-) mice, a model of inflammatory bowel diseases. Br J Nutr, 2009, 101(2): 169-181.
8. Habtemariam S, Belai A. Natural therapies of the inflammatory bowel disease: The case of rutin and its aglycone, quercetin [J]. Mini Rev Med Chem, 2018, 18(3): 234-243.
9. Park J W, Shin N R, Shin I S, et al. Silibinin inhibits neutrophilic inflammation and mucus secretion induced by cigarette smoke via suppression of ERK-SP1 pathway. Phytother Res, 2016, 30(12): 1926-1936.
10. Kim B R, Seo H S, Ku J M, et al. Silibinin inhibits the production of pro-inflammatory cytokines through inhibition of NF-κB signaling pathway in HMC-1 human mast cells. Inflamm Res, 2013, 62(11): 941-950.
11. Beloqui A, Coco R, Memvanga P B, et al. pH-sensitive nanoparticles for colonic delivery of curcumin in inflammatory bowel disease. Int J Pharm, 2014, 473(1/2): 203-212.
12. Zhu L, Gu P, Shen H. Protective effects of berberine hydrochloride on DSS-induced ulcerative colitis in rats. Int Immunopharmacol, 2019, 68: 242-251.
13. Li S, Han J, Wang D S, et al. Sinomenine attenuates chronic inflammatory pain in mice. Metab Brain Dis, 2017, 32(1): 211-219.
14. Tang J, Raza A, Chen J, et al. A systematic review on the sinomenine derivatives. Mini Rev Med Chem, 2018, 18(11): 906-917.
15. Zhou Y, Liu H Y, Song J, et al. Sinomenine alleviates dextran sulfate sodium-induced colitis via the Nrf2/ NQO-1 signaling pathway. Mol Med Rep, 2018, 18(4): 3691-3698.
16. Zhou, J., Tan, L., Xie, J., Lai, Z., Huang, Y., Qu, C., Luo, D., Lin, Z., Huang, P., Su, Z. and Xie, Y., 2017. Characterization of brusatol self-microemulsifying drug delivery system and its therapeutic effect against dextran sodium sulfate-induced ulcerative colitis in mice. Drug delivery, 24(1), pp.1667-1679.
17. Li Q P, Zhai W W, Jiang Q L, et al. Curcumin-piperine mixtures in self-microemulsifying drug delivery system for ulcerative colitis therapy. Int J Pharm, 2015, 490(1/2): 22-31.
18. Zhang D K, Cheng L N, Huang X L, et al. Tetrandrine ameliorates dextran-sulfate-sodium-induced colitis in mice through inhibition of nuclear factor-kappaB activation. Int J Colorectal Dis, 2009, 24(1): 5-12.
19. Monisha B A, Kumar N, Tiku A B. Emodin and its role in chronic diseases. Adv Exp Med Biol, 2016, 928: 47-73.
20. Luo S, Deng X L, Liu Q, et al. Emodin ameliorates ulcerative colitis by the flagellin-TLR5 dependent pathway in mice. Int Immunopharmacol, 2018, 59: 269-275.

21. Ge H, Tang H, Liang Y B, et al. Rhein attenuates inflammation through inhibition of NF-κB and NALP3inflammasome in vivo and in vitro. Drug Des Devel Ther, 2017, 11: 1663-1671.
22. Thippeswamy B S, Mahendran S, Biradar M I, et al. Protective effect of embelin against acetic acid induced ulcerative colitis in rats. Eur J Pharmacol, 2011, 654(1): 100-105.
23. Zhao J, Luo D, Zhang Z, et al. Celastrol-loaded PEG-PCL nanomicelles ameliorate inflammation, lipid accumulation, insulin resistance and gastrointestinal injury in diet- induced obese mice. J Control Release, 2019, 310: 188-197.
24. Jia Z Y, Xu C F, Shen J Q, et al. The natural compound celastrol inhibits necroptosis and alleviates ulcerative colitis in mice [J]. Int Immunopharmacol, 2015, 29(2): 552-559.
25. Zhao Z J, Xiang J Y, Liu L, et al. Parthenolide, an inhibitor of the nuclear factor-κB pathway, ameliorates dextran sulfate sodium-induced colitis in mice. Int Immunopharmacol, 2012, 12(1): 169-174.
26. Zhu Q, Zheng P F, Zhou J Y, et al. Andrographolide affects Th1/Th2/Th17 responses of peripheral blood mononuclear cells from ulcerative colitis patients [J]. Mol Med Rep, 2018, 18(1): 622-626.
27. Zhu Q, Zheng P F, Chen X Y, et al. Andrographolide presents therapeutic effect on ulcerative colitis through the inhibition of IL-23/IL-17 axis. Am J Transl Res, 2018, 10(2): 465-473.
28. Guo Y, Wu X, Wu Q, et al. Dihydrotanshinone I, a natural product, ameliorates DSS-induced experimental ulcerative colitis in mice [J]. Toxicol Appl Pharmacol, 2018, 344: 35-45.
29. Si-Yu, C.A.O., Sheng-Jie, Y.E., Wei-Wei, W.A.N.G., Bing, W.A.N.G., Zhang, T. and Yi-Qiong, P.U., 2019. Progress in active compounds effective on ulcerative colitis from Chinese medicines. Chinese journal of natural medicines, 17(2), pp.81-102.
30. Singh B. Psyllium as therapeutic and drug delivery agent. Int J Pharm, 2007, 334(1/2): 1-14.
31. Laroui H, Dalmasso G, Nguyen H T, et al. Drug-loaded nanoparticles targeted to the colon with polysaccharide hydrogel reduce colitis in a mouse model. Gastroenterology, 2010, 138(3): 843-853.
32. Wu X, Dou Y N, Yang Y, et al. Arctigenin exerts anti-colitis efficacy through inhibiting the differentiation of Th1 and Th17 cells via an mTORC1-dependent pathway. Biochem Pharmacol, 2015, 96(4): 323-336.
33. Dong K, Zeng A G, Wang M L, et al. In vitro and in vivo study of a colon-targeting resin microcapsule loading a novel prodrug, 3,4,5-tributyryl shikimic acid. RSC Adv, 2016, 6(20): 16882-16890.
34. Huang Y F, Zhou J T, Qu C, et al. Anti-inflammatory effects of Brucea javanica oil emulsion by suppressing NF-κB activation on dextran sulfate sodium-induced ulcerative colitis in mice. J Ethnopharmacol, 2017, 198: 389-398.
35. Grzanna R, Lindmark L, Frondoza C G. Ginger: An herbal medicinal product with broad anti-inflammatory actions. J Med Food, 2005, 8(2): 125-132.
36. Zhang M, Viennois E, Prasad M, et al. Edible ginger-derived nanoparticles: A novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. Biomaterials, 2016, 101: 321-340.
37. Brown A C, Shah C, Liu J, et al. Ginger's (Zingiber officinale Roscoe) inhibition of rat colonic adenocarcinoma cells proliferation and angiogenesis in vitro [J]. Phytother Res, 2009, 23(5): 640-645.
38. Kwon K H, Murakami A, Tanaka T, et al. Dietary rutin, but not its aglycone quercetin, ameliorates dextran sulfate sodium-induced experimental colitis in mice: Attenuation of pro-inflammatory gene expression. Biochem Pharmacol, 2005, 69(3): 395-406.
39. Guazelli C F, Fattori V, Colombo B B, et al. Quercetin-loaded microcapsules ameliorate experimental colitis in mice by anti-inflammatory and anti-oxidant mechanisms. J Nat Prod, 2013, 76(2): 200-208.
40. Luo X P, Yu Z L, Deng C, et al. Baicalein ameliorates TNBS-induced colitis by suppressing TLR4/MyD88 signaling cascade and NLRP3 inflammasome activation in mice. Sci Rep, 2017, 7: 16374.
41. Zhang C L, Zhang S, He W X, et al. Baicalin may alleviate inflammatory infiltration in dextran sodium sulfate-induced chronic ulcerative colitis via inhibiting IL-33 expression. Life Sci, 2017, 186: 125-132.
42. Tao F F, Qian C, Guo W J, et al. Inhibition of Th1/Th17 responses via suppression of STAT1 and STAT3 activation contributes to the amelioration of murine experimental colitis by a natural flavonoid glucoside icariin. Biochem Pharmacol, 2013, 85(6): 798-807.
43. Chao L, Zheng P Y, Xia L, et al. Calycosin attenuates dextran sulfate sodium (DSS)-induced experimental colitis. Iran J Basic Med Sci, 2017, 20(9): 1056-1062.
44. Al-Rejaie S S, Abuohashish H M, Al-Enazi M M, et al. Protective effect of naringenin on acetic acid-induced ulcerative colitis in rats. World J Gastroenterol, 2013, 19(34): 5633-5644.
45. He X X, Wei Z K, Wang J J, et al. Alpinetin attenuates inflammatory responses by suppressing TLR4 and NLRP3 signaling pathways in DSS-induced acute colitis. Sci Rep, 2016, 6: 28370.
46. Arafa H M, Hemeida R A, El-Bahrawy A I, et al. Prophylactic role of curcumin in dextran sulfate sodium (DSS)-induced ulcerative colitis murine model. Food Chem Toxicol, 2009, 47(6): 1311-1317.
47. Yadav V R, Suresh S, Devi K, et al. Novel formulation of solid lipid microparticles of curcumin for anti-angiogenic and anti-inflammatory activity for optimization of therapy of inflammatory bowel disease [J]. J Pharm Pharmacol, 2009, 61(3): 311-321.
48. Abdin A A. Targeting sphingosine kinase 1 (SphK1) and apoptosis by colon-specific delivery formula of resveratrol in treatment of experimental ulcerative colitis in rats. Eur J Pharmacol, 2013, 718(1/2/3): 145-153.
49. Yum S, Jeong S, Lee S, et al. Colon-targeted delivery of piceatannol enhances anti-colitic effects of the natural product: Potential molecular mechanisms for therapeutic enhancement. Drug Des Devel Ther, 2015, 9: 4247- 4258.
50. Marín M, María Giner R, Ríos J L, et al. Intestinal anti-inflammatory activity of ellagic acid in the acute and chronic dextrane sulfate sodium models of mice colitis. J Ethnopharmacol, 2013, 150(3): 925-934.
51. Shen P, Zhang Z C, He Y, et al. Magnolol treatment attenuates dextran sulphate sodium-induced murine experimental colitis by regulating inflammation and mucosal damage. Life Sci, 2018, 196: 69-76.
52. Shaker M E, Ashamallah S A, Houssen M E. Celastrol ameliorates murine colitis via modulating oxidative stress, inflammatory cytokines and intestinal homeostasis. Chem Biol Interact, 2014, 210: 26-33.
53. Xiao B, Merlin D. Oral colon-specific therapeutic approaches toward treatment of inflammatory bowel disease. Expert Opin Drug Deliv, 2012, 9(11): 1393- 1407.
54. Collnot E M, Ali H, Lehr C M. Nano- and microparticulate drug carriers for targeting of the inflamed intestinal mucosa. J Control Release, 2012, 161(2): 235-246.
55. Hua S S, Marks E, Schneider J J, et al. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: Selective targeting to diseased versus healthy tissue. Nanomed-Nanotechnol Biol Med, 2015, 11(5): 1117-1132.
56. Lamprecht A, Yamamoto H, Takeuchi H, et al. Nanoparticles enhance therapeutic efficiency by selectively increased local drug dose in experimental colitis in rats. J Pharmacol Exp Ther, 2005, 315(1): 196-202.
57. Lamprecht A, Schäfer U, Lehr C M. Size -dependent bioadhesion of micro- and nanoparticulate carriers to the inflamed colonic mucosa [J]. Pharm Res, 2001, 18(6): 788-793.
58. de Jong W H, Borm P J. Drug delivery and nanoparticles: Applications and hazards. Int J Nanomedicine, 2008, 3(2): 133-149.
59. Powell J J, Faria N, Thomas-McKay E, et al. Origin and fate of dietary nanoparticles and microparticles in the gastrointestinal tract. J Autoimmun, 2010, 34(3): J226- J233.

60. Ma P P, Si X Y, Chen Q B, et al. Oral drug delivery systems for ulcerative colitis therapy: A comparative study with microparticles and nanoparticles. Curr Cancer Drug Targets, 2019, 19(4): 304-311.
61. Zhang M Z, Merlin D. Nanoparticle-based oral drug delivery systems targeting the colon for treatment of ulcerative colitis. Inflamm Bowel Dis, 2018, 24(7): 1401-1415.
62. Nugent S G, Kumar D, Rampton D S, et al. Intestinal luminal pH in inflammatory bowel disease: Possible determinants and implications for therapy with aminosalicylates and other drugs. Gut, 2001, 48(4): 571-577.
63. Raj P M, Raj R, Kaul A, et al. Biodistribution and targeting potential assessment of mucoadhesive chitosan nanoparticles designed for ulcerative colitis via scintigraphy. RSC Adv, 2018, 8(37): 20809-20821.
64. Abdel Ghaffar A M, Radwan R R, Ali H E. Radiation synthesis of poly (starch/acrylic acid) pH sensitive hydrogel for rutin controlled release. Int J Biol Macromol, 2016, 92: 957-964.
65. Jeong Y I, Yŏ R P, Ohno T, et al. Application of Eudragit P-4135F for the delivery of ellagic acid to the rat lower small intestine. J Pharm Pharmacol, 2001, 53(8): 1079-1085.
66. Xiong H, Tian L, Zhao Z, et al. The sinomenine enteric-coated microspheres suppressed the TLR/NF-κB signaling in DSS-induced experimental colitis. Int Immunopharmacol, 2017, 50: 251-262.
67. Chourasia M K, Jain S K. Polysaccharides for colon targeted drug delivery. Drug Deliv, 2004, 11(2): 129-148.
68. Basit A W, Short M D, McConnell E L. Microbiota- triggered colonic delivery: Robustness of the polysaccharide approach in the fed state in man. J Drug Target, 2009, 17(1): 64-71.
69. Pinto J F. Site-specific drug delivery systems within the gastrointestinal tract: From the mouth to the colon. Int J Pharm, 2010, 395(1/2): 44-52.
70. Castangia I, Nácher A, Caddeo C, et al. Therapeutic efficacy of quercetin enzyme-responsive nanovesicles for the treatment of experimental colitis in rats. Acta Biomater, 2015, 13: 216-227.
71. Wang Q S, Wang G F, Zhou J, et al. Colon targeted oral drug delivery system based on alginate-chitosan microspheres loaded with icariin in the treatment of ulcerative colitis. Int J Pharm, 2016, 515(1/2): 176-185.
72. Gou S Q, Huang Y M, Wan Y, et al. Multi-bioresponsive silk fibroin-based nanoparticles with on-demand cytoplasmic drug release capacity for CD44-targeted alleviation of ulcerative colitis. Biomaterials, 2019, 212: 39-54.
73. Kucharzik T, Lugering A, Yan Y T, et al. Activation of epithelial CD98 glycoprotein perpetuates colonic inflammation. Lab Invest, 2005, 85(7): 932-941.
74. Xiao B, Zhang Z, Viennois E, et al. Combination therapy for ulcerative colitis: Orally targeted nanoparticles prevent mucosal damage and relieve inflammation. Theranostics, 2016, 6(12): 2250-2266.
75. Zhang M Z, Wang X Y, Han M K, et al. Oral administration of ginger-derived nanolipids loaded with siRNA as a novel approach for efficient siRNA drug delivery to treat ulcerative colitis. Nanomedicine (Lond), 2017, 12(16): 1927-1943.
76. Chen Q B, Gou S Q, Ma P P, et al. Oral administration of colitis tissue-accumulating porous nanoparticles for ulcerative colitis therapy. Int J Pharm, 2019, 557: 135-144.
77. Dou Y X, Zhou J T, Wang T T, et al. Self- nanoemulsifying drug delivery system of bruceine D: A new approach for anti-ulcerative colitis. Int J Nanomedicine, 2018, 13: 5887-5907.
78. Chen Q B, Si X Y, Ma L J, et al. Oral delivery of curcumin via porous polymeric nanoparticles for effective ulcerative colitis therapy. J Mater Chem B, 2017, 5(29): 5881-5891.
79. Xiao B, Si X Y, Zhang M Z, et al. Oral administration of pH-sensitive curcumin-loaded microparticles for ulcerative colitis therapy. Colloids Surf B Biointerfaces, 2015, 135: 379-385.
80. Varshosaz J, Minaiyan M, Khaleghi N. Eudragit nanoparticles loaded with silybin: A detailed study of preparation, freeze-drying condition and in vitro/in vivo evaluation. J Microencapsul, 2015, 32(3): 211-223.
81. Yen C C, Chen Y C, Wu M T, et al. Nanoemulsion as a strategy for improving the oral bioavailability and anti-inflammatory activity of andrographolide. Int J Nanomedicine, 2018, 13: 669-680.
82. Badamaranahalli S S, Kopparam M, Bhagawati S T, et al. Embelin lipid nanospheres for enhanced treatment of ulcerative colitis-Preparation, characterization and in vivo evaluation. Eur J Pharm Sci, 2015, 76: 73-82.