PERSPECTIVE
Traditional Medicine Research 2026;11(2):14. https://doi.org/10.53388/TMR20240326001

Recent advances in shikonin nanoformulations for managing inflammation-related disease

Ting-Ting Zuo[1], Jun-Jie Zhang[2*], Derya bal Altuntaş[3], Dong-Liang Yang[4*], Chao Zhang[5*]

[1]College of Biological Sciences and Technology, Yili Normal University, Yining 835000, China. [2]School of Fundamental Sciences, Bengbu Medical University, Bengbu 233030, China. [3]Faculty of Engineering and Architecture, Department of Bioengineering, Recep Tayyip Erdogan University, Rize 53100, Turkey. [4]State Key Laboratory of Flexible Electronics (LoFE) & Institute of Advanced Materials (IAM), School of Physical and Mathematical Sciences, Nanjing Tech University, Nanjing 211816, China. [5]Department of Neurosurgery, Zhujiang Hospital, Southern Medical University, Guangzhou 510282, China.

[*]**Correspondence to:** Jun-Jie Zhang, School of Fundamental Sciences, Bengbu Medical University, No. 2600, Donghai Road, Bengbu 233030, China. E-mail: zhangjj@bbmu.edu.cn. Dong-Liang Yang, State Key Laboratory of Flexible Electronics (LoFE) & Institute of Advanced Materials (IAM), School of Physical and Mathematical Sciences, Nanjing Tech University, No. 5, Xinmofan Avenue, Nanjing 211816, China. E-mail: yangdl1023@njtech.edu.cn. Chao Zhang, Department of Neurosurgery, Zhujiang Hospital, Southern Medical University, No. 253, Gongye Dadao Zhong, Guangzhou 510282, China. E-mail: czhangsinap@163.com.

Author contributions

Zuo TT drafted the manuscript. Zhang JJ conducted the literature search. bal Altuntaş D led the data visualization. Yang DL reviewed and edited the manuscript. Zhang C contributed to the conceptualization and study design.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (82373393), Xinjiang Uygur Autonomous Region "Tianchi Yingcai" Project (2023TCYCQNBS02); Xinjiang Uygur Autonomous Region Colleges and Universities Basic Research Operating Expenses Scientific Research Project (XJEDU2022P106).

Peer review information

Traditional Medicine Research thanks all anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations

IBD, inflammatory bowel disease; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; TGF-β, transforming growth factor-β; NF-κB, nuclear factor-κB; MAPK, mitogen-activated protein kinase; LPS, lipopolysaccharide; CS, chitosan; HA, hyaluronic acid; ALG, alginate; GUM, utilized polysaccharides.

Citation

Zuo TT, Zhang JJ, bal Altuntaş D, Yang DL, Zhang C. Recent advances in shikonin nanoformulations for managing inflammation-related disease. *Tradit Med Res*. 2026;11(2):14. doi: 10.53388/TMR20240326001.

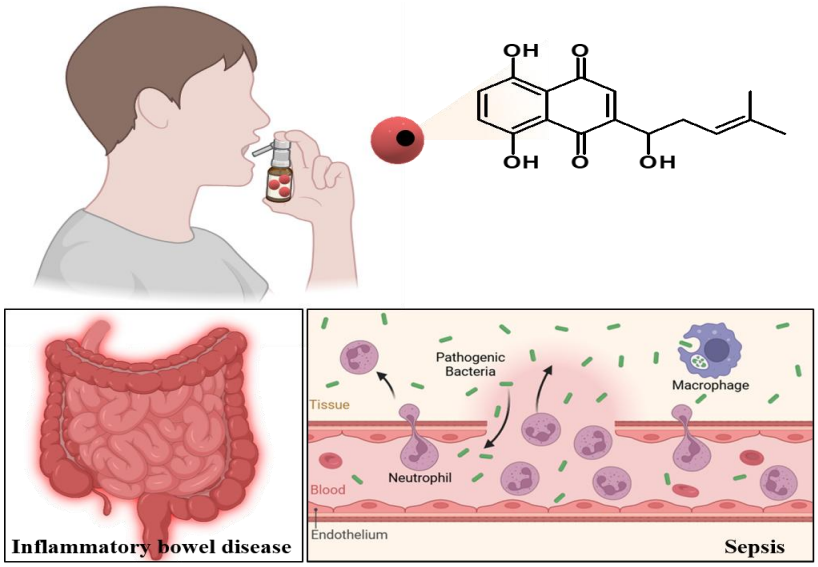
Executive editor: Meng-Meng Song.

Received: 26 March 2025; **Revised:** 06 May 2025; **Accepted:** 21 May 2025; **Available online:** 06 June 2025.

Abstract

Shikonin, a naphthoquinone compound derived from the root of *Lithospermum erythrorhizon*, has been extensively studied for its antibacterial, antioxidant, and anti-inflammatory properties. Increasing evidence highlights its potential in treating inflammation-related diseases. However, its clinical application is hindered by challenges such as poor water solubility, rapid metabolism in vivo, and other limitations. Recent advancements have demonstrated that encapsulating shikonin within nanocarriers can significantly enhance its water solubility and pharmacokinetic profile. Building on this, this perspective paper outlines the current landscape of inflammation treatment, explores the anti-inflammatory mechanisms of shikonin, reviews the latest progress in shikonin-based nanomaterials for anti-inflammatory applications, and discusses the challenges and future directions for the clinical translation of shikonin nanoformulations.

Keywords: shikonin; nanomedicine; inflammation-related diseases



Traditional Medicine Research 2026;11(2):14. https://doi.org/10.53388/TMR20240326001

Highlights

The anti-inflammatory mechanism of shikonin was discussed.
Recent advances of shikonin nanoformulations in inflammatory-related diseases was summarized.
The opportunities and challenges of shikonin nanoformulations was discussed.

Medical history of objective

The medicinal properties of *Lithospermum erythrorhizon* were first documented in the Han Dynasty's *Shennong Bencao Jing* (compiled around the 1st century C.E.). *Compendium of Materia Medica* (compiled in 1593 C.E.) by Shizhen Li of the Ming Dynasty further confirmed its anti-inflammatory applications. Modern medical identified shikonin as the plant's primary bioactive compound, exhibiting diverse pharmacological activities including antioxidant, antibacterial, antithrombotic, and anti-inflammatory effects, along with wound-healing promotion.

Introduction

Inflammation is a critical component of both innate and adaptive immunity, serving as a key defense mechanism against endogenous and exogenous injuries [1]. During an inflammatory response, various immune cells (e.g., white blood cells, macrophage) and plasma proteins (e.g., cytokines, complement proteins) are recruited and activated at the site of infection or injury [2]. The hallmark characteristics of the inflammatory response include redness, fever, swelling, and pain [3]. However, when the immune system becomes dysfunctional, leading to excessive or prolonged inflammation, it can result in chronic and acute diseases such as multiple sclerosis, chronic asthma, psoriasis, rheumatoid arthritis, inflammatory bowel disease (IBD), and sepsis [4, 5]. These conditions not only severely impact patients' quality of life but are also becoming increasingly prevalent in aging societies, posing a significant global public health challenge.

During inflammation, immune cells such as macrophages, lymphocytes, eosinophils, and neutrophils are activated and produce a variety of inflammatory mediators. These include pro-inflammatory factors like interleukin-1β (IL-1β), IL-6, interferon-γ, tumor necrosis factor-α (TNF-α), and IL-8, as well as anti-inflammatory factors such as IL-10 and transforming growth factor-β (TGF-β). In addition to inflammatory mediators, several signaling pathways, such as the mitogen-activated protein kinase (MAPK), nuclear factor-κB (NF-κB), and Janus kinase/signal transduction and transcriptional activator signaling pathways, play critical roles in regulating inflammation [6]. Modulating these inflammatory factors and pathways can intervene in the inflammatory response, thereby achieving therapeutic effects.

Currently, several major classes of drugs, including corticosteroids, non-steroidal anti-inflammatory drugs, and biologics, are used to treat inflammation-related diseases. However, these therapies have notable limitations. For instance, corticosteroids are often associated with side effects such as hyperglycemia, hypertension, muscle weakness, increased susceptibility to infections, osteoporosis, glaucoma, and growth suppression. Non-steroidal anti-inflammatory drugs may cause platelet dysfunction, gastrointestinal ulcers, and bleeding, while biologic therapies are costly and carry risks of cardiovascular complications [7]. Consequently, there is an urgent need for the development of novel anti-inflammatory drugs.

Previous studies have demonstrated that many natural products possess significant anti-inflammatory properties. In fact, natural products inspired the synthesis of the first anti-inflammatory drug, aspirin. Since then, natural products have garnered considerable attention as a valuable source of anti-inflammatory agents. Compared to traditional synthetic drugs, natural product-based anti-inflammatory therapies offer advantages such as fewer side effects, diverse biological activities, and the ability to modulate multiple targets in the inflammatory response. One such natural compound is shikonin (5,8-dihydroxy-2-((1R)-1-hydroxy-4-methyl-3-pentenyl)-1,4-naphthoquinone), a bioactive substance derived from the roots of *Lithospermum erythrorhizon*. Shikonin has been widely studied for its antibacterial, antiviral, antitumor, antioxidant, and anti-inflammatory properties and has been used in traditional medicine to treat diseases such as wounds, measles, and autoimmune-mediated inflammatory diseases [8]. However, as a hydrophobic natural molecule, shikonin faces several challenges, including poor solubility, rapid intestinal absorption, a significant "first-pass" effect, and fast clearance rates, all contributing to low oral bioavailability [9]. Additionally, shikonin can cause severe skin sensitization, induce erythrocyte hemolysis, and interact with other drugs through metabolic enzymes, posing potential toxicity risks. These limitations have significantly hindered its clinical application.

In recent years, advancements in nanomedicine have offered promising solutions to these challenges [10]. Nanomedicine provides unique advantages, such as enhancing the water solubility of drugs, prolonging drug circulation times, improving bioavailability, enabling controlled drug release, enhancing therapeutic efficacy, and reducing adverse effects [11]. Numerous evidences have confirmed that nanomedical drug delivery systems can distinctly enhance the bioavailability and efficacy of drugs without requiring chemical modifications [12]. Notably, several FDA-approved nanomaterials have shown encouraging results in antimicrobial and anticancer therapies [13]. As a result, nanodrug delivery systems are considered a highly effective strategy for improving the therapeutic effect of drug. To address the limitations of shikonin, researchers have developed various nanodrug delivery systems, including liposomes, polymeric micelles, nanoparticles, nanogels, nanoemulsions, and hybrid advanced drug delivery nanosystems, to enable efficient delivery and clinical application of shikonin. This review systematically discusses the anti-inflammatory mechanisms of shikonin, highlights recent advancements in shikonin nanoformulations for anti-inflammatory applications (Figure 1), and discusses the challenges and future directions for the development of shikonin-based nanoformulations.

Literature search methodology

The references for this article were systematically retrieved from Google Scholar using targeted keyword combinations. For the section on "Shikonin Nanoformulation for Inflammation-Related Disease Management", the search terms "shikonin, nano, and inflammation" were employed. For other sections, the keyword combination was refined to "shikonin and inflammation" to maintain focus on nanotherapeutic applications. To ensure the inclusion of current and high-impact studies, search filters were applied to prioritize publications from the last decade and those with significant citation counts.

Anti-inflammatory effects of shikonin

Regulation of immune cells

T lymphocytes (T cells) play a vital role in immune response and immune regulation. Shikonin can play an immunosuppressive role by inhibiting the proliferation of T cells and reducing the secretion of pro-inflammatory cytokines (such as IL-12, IL-6, TNF-α, etc.) from Th1 cells. Shikonin inhibits T cell differentiation to Th17 by inhibiting LR4/MyD88 pathway, further relieving Th17-mediated inflammation [14]. The treatment qualities of shikonin may be related to the reduction of skin inflammatory response by $CD4^+CD25^+FoxP3^+$regulatory T cells in the collagen-induced arthritis [14]. Moreover, shikonin exerts an immunoprotective effect by stimulating $CD4^+Foxp3^+$Treg differentiation, increasing induced regulatory T cells, inhibiting T cell activation and the secretion of pro-inflammatory cytokines in the allograft patients [15]. In the regulation of B lymphocytes (B cells), shikonin suppresses the activity of M2 pyruvate kinase, restrains the proliferation of B cells and the production of immunoglobulin, further reducing atherosclerosis [16].

Traditional Medicine Research 2026;11(2):14. https://doi.org/10.53388/TMR20240326001

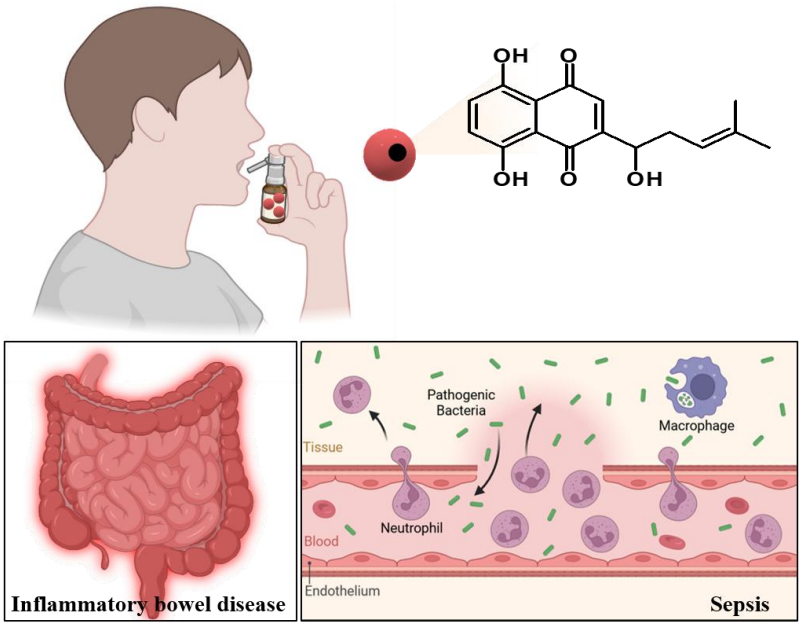


Figure 1 Shikonin nanoformulations for the treatment of IBD and sepsis

Regulation of inflammatory factors

When the body suffers from bacterial infection or other pathological stimulation, the immune system is activated and releases a series of inflammatory factors. Among them, IL-1β, IL-6, IL-17, and TNF-α play a crucial role in the pathogenesis of autoimmune diseases, while IFN-β, IL-10, TGF-β and other anti-inflammatory cytokines can alleviate autoimmune diseases [17, 18]. Recently, studies have found that shikonin relieves inflammatory responses by down-regulating pro-inflammatory cytokines and up-regulating anti-inflammatory cytokines. For example, TNF-α that produced primarily by activated macrophages, promotes inflammation by adjusting the generation of chemokines, cytokines, COX-2, iNOS, and some adhesion molecules. These processes are involved in the occurrence of immunoinflammatory diseases, including chronic hepatitis, rheumatoid arthritis, psoriasis, IBD, atherosclerosis, and pulmonary fibrosis. IL-10 can regulate T cells, B cells and other immune cells to play an anti-inflammation and anti-angiogenesis role. Studies have found that shikonin can reduce IBD damage by reducing the levels of inflammatory cytokines IL-1β, IL-6 and TNF-α, as well as increasing the levels of IL-10 [19]. These findings indicate that shikonin may also play a therapeutic effect by regulation inflammatory cytokine content in the immune system.

Regulation of signal pathway

The inflammatory response is also regulated by NF-κB, STAT3 and MAPK signaling pathways [20–22]. Studies have shown that shikonin inhibits the phosphorylation of IκB-α and interferes with (i.e. down-regulates) the NF-κB signaling pathway to alleviate lipopolysaccharide (LPS)-induced pulmonary inflammation [20]. In the treatment of psoriasis, shikonin blocks the secretion of JAK/STAT3-related cytokines, thus interfering the STAT3 signaling pathway and reducing the production of keratin K17 in keratinocytes [23, 24]. By reducing the expression of K17 antigen, the activation of T cells is reduced, thereby avoiding the recurrence of psoriasis. Furthermore, shikonin was found to counteract IL-17-induced downregulation of the tumor suppressor CCAAT/enhancer-binding protein δ in human immortal keratinocytes (HaCaT), thereby preventing excessive keratinocyte proliferation and exerting therapeutic effects [24]. The MAPK signaling pathway is involved in the regulation of inflammation related to diabetes and rheumatoid arthritis. Previous evidences indicate that shikonin suppresses NF-κB/MAPK signaling pathway, interferes with the phosphorylation of p38, ERK and JNK proteins, and reduces D-galactose-induced neuroinflammation in mice [21, 25]. These results suggest that shikonin can also act on inflammatory signaling pathways to exert an anti-inflammatory effects. However, because shikonin affects a broad range of inflammatory pathways, the interactions between them remain poorly understood. As a result, most current studies focus only on analyzing individual pathways, changes in inflammatory factors, and immune cell phenotypes.

Shikonin nanoformulation for inflammation-related disease management

IBD is a chronic gastrointestinal disorder characterized by a reduced pH environment in the inflamed colon, increased secretion of inflammatory cells, and elevated levels of pro-inflammatory cytokines [26]. Recruited immune cells, such as macrophages, neutrophils, and monocytes, release inflammatory cytokines and oxygen free radicals, leading to secondary tissue damage due to the action of oxidative stress [27]. In addition, these inflammatory factors further exacerbate the inflammatory response. Current therapeutic strategies for IBD primarily focus on alleviating inflammatory symptoms.

Recently, Gao group developed a pH-responsive nanodelivery system (Shik@CS/HA/ES) for the targeted release of shikonin (Shik) to treat IBD. Shik was loaded into chitosan (CS) nanoparticles via an ion-crosslinking strategy, followed by coating with CD44-functionalized hyaluronic acid (HA) and the pH-responsive, colitic-soluble polymer Eudragit S100 (ES100) through electrostatic interactions (Figure 2A) [28]. Leveraging the properties of ES100, Shik@CS/HA/ES degrades in the colon, releasing Shik@CS/HA. The CD44 on the nanoparticle surface then targets the CD44 receptors on the macrophages, enhancing the enrichment of Shik@CS/HA in RAW 264.7 mouse macrophages. In a mouse IBD model, treatment with Shik@CS/HA/ES significantly reduced the inflammatory response, as evidenced by decreased infiltration of inflammatory cells and reduced expression of pro-inflammatory factors (e.g., IL-6, IL-1β, TNF-α, COX-2, and iNOS decreased from 480 pg/g to 200 pg/g, 950 pg/g to 300 pg/g, 3,500 pg/g to 1,300 pg/g, 700 U/L to 200 U/L, and 175 pg/g to 105 pg/g, respectively), while increasing the expression of anti-inflammatory factors (e.g., IL-10 increased from 800 pg/g to 3,000 pg/g, while TGF-β rose from 200 pg/g to 700 pg/g) in colonic sites. Consequently, Shik@CS/HA/ES treatment markedly improved the integrity of the intestinal mucosa in mice. In a follow-up study, the authors incorporated calcium ions (Ca^{2+}) and sodium alginate (ALG) as protective agents to prevent the premature release of Shik@CS/HA in the stomach [29]. Shik@CS/HA/ALG-Ca^{2+} was designed to target delivery Shik@CS/HA due to ALG will dissolve in the intestine (pH

7.4). Therefore, oral administration of Shik@CS/HA/ALG-Ca^{2+} not only reduced the expression of pro-inflammatory factors (e.g., IL-6, IL-1β, and TNF-α decreased from 580 pg/g to 220 pg/g, 940 pg/g to 470 pg/g, 4,100 pg/g to 1,900 pg/g, respectively) and enhanced anti-inflammatory responses (e.g., IL-10 increased from 760 pg/g to 2,000 pg/g, while TGF-β rose from 250 pg/g to 720 pg/g) but also inhibited the polarization of immune cells toward the M1 phenotype, promoting the restoration of normal cells and demonstrating significant therapeutic effects against IBD. While the cumbersome and complex fabrication processes of Shik@CS/HA/ES and Shik@CS/HA/ALG-Ca^{2+} may hinder their scalability and industrial applicability.

In addition to leveraging the physiological properties of the gut, the elevated levels of ROS in inflamed regions can also serve as a trigger for targeted drug release. For instance, Hu, et al. utilized polysaccharides (GUM) from tragacanth gum as a hydrogen peroxide-responsive unit (Figure 2B) [9]. They synthesized nanocomposites by the coordination effect between iron ions and polyphenol units on GUM, encapsulating Shik within the nanoparticles to form Shik-Fe@GUM. Upon oral administration, Shik-Fe@GUM adheres to the colon membrane, stagnates in the colon, and exerts anti-inflammatory effect (e.g., TNF-α, IL-6, and IL-1β content in the serum decreased from 800 pg/mL to 200 pg/mL, 2,750 pg/mL to 1,100 pg/mL, 500 pg/mL to 170 pg/mL, respectively). Elevated hydrogen peroxide levels at the inflammatory site can degrade GUM polysaccharides. Therefore, in vivo treatment with Shik-Fe@GUM significantly reduced ROS levels, IL-17A inflammatory factor, and Th17 cell populations. Informatics studies further revealed that Shik-Fe@GUM inhibits the IL-17RA signaling pathway, thereby mitigating the inflammatory response. As a result, oral administration of Shik-Fe@GUM effectively restored the colonic mucosal barrier by alleviating intestinal inflammation.

The regulation of inflammatory responses is not limited to inflammatory factors and signaling pathways but also involves inflammasomes. Recently, Cardoso, et al. developed a nanogel carrier composed of FDA-approved zein and HA for Shik delivery. HA-Zein-Shik nanogels can specifically interact with HA-binding receptors on macrophages, enabling targeted delivery. When human THP-1-derived macrophages ingested HA-Zein-SK nanogels, inflammasome activation was inhibited significantly. This effect was further confirmed in a LPS and nigericin-induced macrophage stimulation model, where HA-Zein-SK nanogels reduced inflammasome activation. Building on this concept, Qiao's team synthesized Zn-Shik-PEG NPs through the self-assembly of Shik and zinc ions (Figure 2C) [30]. These nanoparticles inhibit inflammatory responses by suppressing the nuclear factor e2-related factor 2/heme oxygenase-1 signaling pathway to clear intracellular ROS, thereby alleviating excessive inflammation reaction. Furthermore, in LPS-activated macrophages, Zn-Shik-PEG NPs not only reduced the expression of inflammatory factors (e.g., TNF-α levels declined sharply from 1,500 pg/mL to about 470 pg/mL, IL-6 dropped from 2,400 pg/mL to around 300 pg/mL) but also mitigated LPS-induced inflammatory damage by downregulating the adenosine monophosphate (amp)-activated protein kinase/silent information regulator two 1 (AMPK/SIRT1) signaling pathway. As a result, Zn-Shik-PEG NPs significantly reduced systemic inflammation in sepsis models while alleviating organ damage in septic patients. Although Zn-Shik-PEG NPs and Shik-Fe@GUM demonstrate significant anti-inflammatory effect, the incorporation of inorganic metal ions may elicit safety concerns.

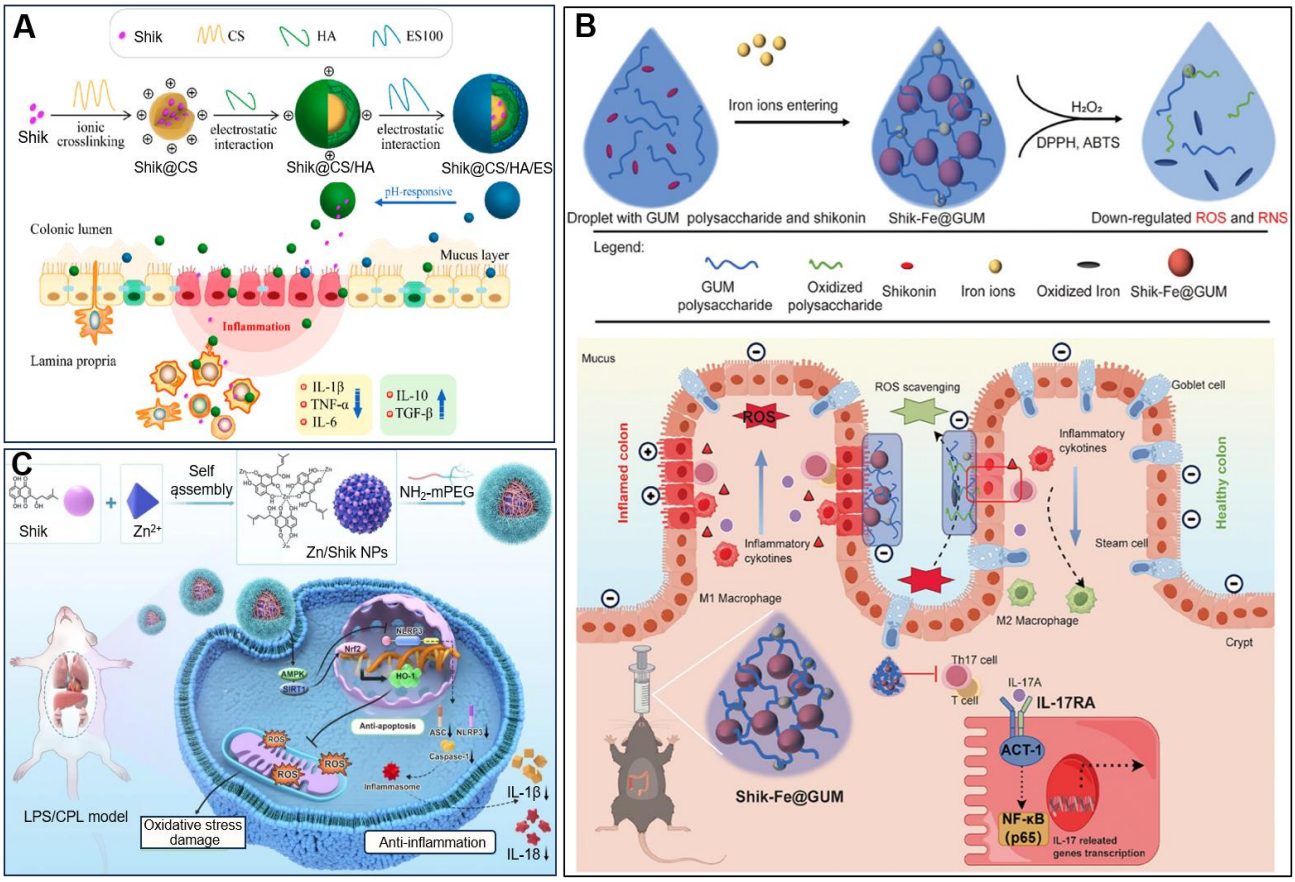


Figure 2 Shikonin nanoformulations for IBD and sepsis treatment. (A) Shik@CS/HA/ES for IBD treatment. (B) Shik-Fe@GUM for IBD management via IL-17RA signaling pathway. (C) Zn-Shik-PEG NPs for sepsis management via NLRP3 inflammasome, the nuclear factor e2-related factor 2/heme oxygenase-1 signaling pathway and AMPK/SIRT1 signaling pathway regulation. Shik, shikonin; CS, chitosan; HA, hyaluronic acid; ES100, Eudragit S100; ALG, sodium alginate; GUM, polysaccharides; LPS, lipopolysaccharide; CLP, cecal ligation and puncture.

In addition to IBD and sepsis, Shik nanoformulation has also been applied in psoriasis treatment. Li, et al. developed a Shik@PLGA-gel by dispersing Shik@PLGA-loaded PLGA (Poly(lactic-co-glycolic acid)) NPs in Carbopol 934 gel. in vivo evaluation indicated that Shik@PLGA-gel significantly reduced inflammatory factor levels (e.g., the mRNA expression levels of IL-1β, IL-17F, IL-17A, IL-22, and TNF-α decreased more than threefold) and suppressed the inflammatory response at the lesion site, thereby minimizing skin damage in psoriasis mice and enhancing therapeutic efficacy [31]. To enhance the application potential of Shik@PLGA-gel in broader therapeutic contexts, future research should prioritize comprehensive release kinetic characterization of Shik. As shown in Table 1 [9, 28–31], Shik nanoformulations exhibit great potential in treating IBD and other inflammatory diseases by targeting multiple pathways and leveraging nano delivery systems.

Challenges and perspective

Due to its potent anti-inflammatory properties, Shik has garnered significant attention in the development of nanomedicine. Shik nanoformulation exhibits superior characteristics compared to free Shik, including enhanced hydrophilicity and stability, improved bioavailability, prolonged circulation time, strong targeting capabilities, and efficient cellular uptake. Shik-based nanoformulations exhibit excellent biocompatibility and safety, demonstrating promising therapeutic efficacy in treating inflammation-related diseases. Despite the considerable progress and promising clinical applications of Shik-based anti-inflammatory nanoagents, several challenges remain for their future clinical translation.

The biological activity and pharmacokinetics of nanoformulations are significantly influenced by their size, surface properties, and stability. Therefore, ensuring the consistency of physicochemical properties (such as size, particle size distribution, and surface charge) across different batches during large-scale production is crucial for subsequent efficacy evaluation and parameter optimization. For instance, the size and morphology of nanomaterials critically influence both their skin permeability and systemic toxicity [32, 33]. In addition, compared to curcumin and resveratrol nanomedicines, shikonin nanoformulations demonstrate superior anti-inflammatory efficacy, exhibiting broader pathway modulation and greater responsiveness to inflammatory microenvironmental cue [34]. The majority of current studies employ polymeric nanoparticles as Shik carriers, primarily due to their superior stability, higher drug-loading capacity, and tunable drug-release kinetics compared to micelles and liposomes [35]. These advantages significantly enhance the prospects for their commercial development and clinical translation.

Previous studies have preliminarily confirmed the biocompatibility of Shik-based nanotherapeutics, most validations have been conducted at the cellular level or through short-term in vivo toxicity studies. Long-term toxicity assessments are still lacking. For instance, while PEGylation enhances the aqueous solubility of Shik, it may induce nephrotoxic effects. Consequently, comprehensive toxicity studies-including both acute high-dose and chronic low-dose evaluations-are critically warranted [36]. Additionally, the preparation process of Shik-based nanoformulations often involves organic solvents, and the potential risks posed by residual solvents cannot be ignored. Future preparations should consider using FDA-approved biomaterials for nanocarrier construction to deliver Shik. Moreover, surface modifications of nanomaterials should be implemented to prevent protein adsorption and the formation of protein coronas, which can affect the stability and biological activity of the nanotherapeutics, during in vivo applications. For instance, coating nanoparticles with hybrid membranes that derived from immune cells and erythrocytes enhance their inflammatory targeting capability while prolonging blood circulation time and minimizing clearance [37].

The ability of nanodelivery systems to overcome various biological barriers (such as the intestinal mucosal barrier, blood-brain barrier, and immune system recognition and clearance) and effectively deliver anti-inflammatory agents to the site of inflammation is critical. For example, leveraging the autonomous propulsion of nanomotors (e.g., magnetically-, optically-, or acoustically-driven systems) enables targeted navigation to lesion sites while overcoming biological barriers (e.g., mucosal and vascular barriers), thereby enhancing Shik delivery efficiency [38, 39].

Currently, the anti-inflammatory efficacy of Shik-based nanotherapeutics is primarily evaluated at the cellular level or in mouse models. However, due to interspecies differences, further validation is required to determine whether Shik nanoformulations retain high anti-inflammatory activity in humans. First, the complex internal microenvironment significantly impacts their ability to accumulate at inflammatory sites, which complicates the assessment of their anti-inflammatory efficacy. Second, the multicomponent nature of current Shik nanoformulations presents significant challenges for both synthesis and scalable production, severely limiting their commercial viability. Third, substantial interpatient variability poses difficulties in establishing standardized efficacy evaluation protocols during preclinical and clinical research. Fourth, from a commercial standpoint, the development of novel nanotherapeutics requires extensive time and financial investment, rendering both pharmaceutical companies and government funding bodies highly risk-averse.

Despite these challenges, we propose that interdisciplinary collaboration among clinicians, industrial pharmacologists, and translational researchers can systematically address these limitations to accelerate the clinical adoption of Shik-based nanomedicines.

Table 1 Summary of Shik-based nanoformulation for inflammatory disease treatment

Dosage forms	Composition	Disease	Therapeutic target	Outcome	Ref
Nanoparticle	Shik@CS/HA/ES	IBD	No relative investigation	IL-1β, IL-6, and TNF-α level decrease, IL-10 and TGF-β increase, improving the intestinal barrier.	[28]
Nanoparticle	Shik@CS/HA/ALG-Ca^{2+}	IBD	Inhibiting the polarization of macrophages towards M1	IL-1β, IL-6, and TNF-α level decrease, IL-10 and TGF-β increase, repairing intestinal barrier function.	[29]
Nanoparticle	Shik-Fe@GUM	IBD	IL-17RA-related pathways	TNF-α, IL-1β and IL-6 level decrease, preventing colonic damages.	[9]
Nanoparticle	Zn-Shik-PEG NPs	Sepsis	AMPK/SIRT1 pathway	IL-6, and TNF-α level decrease, preventing major organ failure.	[30]
Gel	Shik@PLGA-gel	Psoriasis	NF-κB signaling pathway	IL-1β, IL-17F, IL-17A, IL-22, and TNF-α level decrease, minimizing inflammatory cells infiltration.	[31]

IBD, inflammatory bowel disease; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α; TGF-β, transforming growth factor-β.

References

1. Coll RC, Schroder K. Inflammasome components as new therapeutic targets in inflammatory disease. *Nat Rev Immunol.* 2024;25(1):22–41. Available at: http://doi.org/10.1038/s41577-024-01075-9
2. Man SM, Kanneganti TD. Innate immune sensing of cell death in disease and therapeutics. *Nat Cell Biol.* 2024;26(9):1420–1433. Available at: http://doi.org/10.1038/s41556-024-01491-y
3. Libby P, Smith R, Rubin EJ, Glassberg MK, Farkouh ME, Rosenson RS. Inflammation unites diverse acute and chronic diseases. *Eur J Clin Invest.* 2024;54(11):e14280. Available at: http://doi.org/10.1111/eci.14280
4. Markovic MD, Panic VV, Pjanovic RV. Polymeric Nanosystems: A Breakthrough Approach to Treating Inflammation and Inflammation Related Diseases. *Biopolymers.* 2025;116(3):e70012. Available at: http://doi.org/10.1002/bip.70012
5. Monteleone G, Moscardelli A, Colella A, Marafini I, Salvatori S. Immune-mediated inflammatory diseases: Common and different pathogenic and clinical features. *Autoimmun Rev.* 2023;22(10):103410. Available at: http://doi.org/10.1016/j.autrev.2023.103410
6. Jain D, Singh K, Gupta P, et al. Exploring synergistic benefits and clinical efficacy of turmeric in management of inflammatory and chronic diseases: A traditional Chinese medicine based review. *Pharmacol Res Mod Chin Med.* 2025;14:100572. Available at: http://doi.org/10.1016/j.prmcm.2025.100572
7. Dai Z, Yang H, Yin P, et al. Applications of Cyclodextrin-Based Drug Delivery Systems in Inflammation-Related Diseases. *Pharmaceutics.* 2025;17(3):378. Available at: http://doi.org/10.3390/pharmaceutics17030378
8. Biswal S, Biswal BK. Bioavailability and Pharmacological Properties of Shikonin – A Phytocompound from Lithospermum Erythrorhizon. *Chem Select.* 2024;9(45):e202403504. Available at: http://doi.org/10.1002/slct.202403504
9. Hu JL, Wang XF, Sun Q, et al. A Polysaccharide Metal Phenolic Network Nanocomposite for Theranostic Applications in Inflammatory Bowel Disease. *Adv Funct Mater.* 2025;35(11):2416918. Available at: http://doi.org/10.1002/adfm.202416918
10. Huang YJ, Guo XH, Wu Y, et al. Nanotechnology's frontier in combatting infectious and inflammatory diseases: prevention and treatment. *Signal Transduct Target Ther.* 2024;9(1):34. Available at: http://doi.org/10.1038/s41392-024-01745-z
11. Opoku-Damoah Y, Zhang R, Ta HT, Xu ZP. Therapeutic gas-releasing nanomedicines with controlled release: Advances and perspectives. *Exploration (Beijing).* 2022;2(5):20210181. Available at: https://doi.org/10.1002/EXP.20210181
12. Wu Y, Hu C, Wang YB. Recent advances in the application of biomimetic nanomedicines in disease treatment. *Biomed Eng Commun.* 2022;1(1):4. Available at: http://doi.org/10.53388/BMEC2022004
13. Asadi A, Obidiro O, Elesho R, Agbaje K, Kochakzade M, Karla PK. Recent advances and FDA approvals in nanoformulations for drug delivery. *J Nanopart Res.* 2025;27:12. Available at: http://doi.org/10.1007/s11051-024-06199-6
14. Dai QM, Li J, Yun Y, Wang JW. Toll-Like Receptor 4 – Myeloid Differentiation Primary Response Gene 88 Pathway Is Involved in the Shikonin Treatment of CIA by Regulating Treg/Th17 Expression. *Evid-Based Complement Altern Med.* 2018;2018(1):2428546. Available at: http://doi.org/10.1155/2018/2428546
15. Zeng Q, Qiu F, Chen Y, et al. Shikonin Prolongs Allograft Survival via Induction of $CD4^+FoxP3^+$ Regulatory T Cells. *Front Immunol.* 2019;10:652. Available at: http://doi.org/10.3389/fimmu.2019.00652
16. Deng JC, Lv SL, Liu HY, et al. Homocysteine Activates B Cells via Regulating PKM2-Dependent Metabolic Reprogramming. *J Immunol.* 2017;198(1):170–183. Available at: http://doi.org/10.4049/jimmunol.1600613
17. Yasmeen F, Pirzada RH, Ahmad B, Choi B, Choi S. Understanding Autoimmunity: Mechanisms, Predisposing Factors, and Cytokine Therapies. *Int J Mol Sci.* 2024;25(14):7666. Available at: http://doi.org/10.3390/ijms25147666
18. Nakamura Y, Imai K, Umeda M. Shikonin affects wound healing and anti-inflammatory expression of human gingival epithelial cells. *J Osaka Dent Univ.* 2025;59(1):51–57. Available at: http://doi.org/10.18905/jodu.59.1_51
19. Han H, Sun W, Feng L, et al. Differential relieving effects of shikonin and its derivatives on inflammation and mucosal barrier damage caused by ulcerative colitis. *PeerJ.* 2021;9:e10675. Available at: http://doi.org/10.7717/peerj.10675
20. Liang D, Sun Y, Shen Y, et al. Shikonin exerts anti-inflammatory effects in a murine model of lipopolysaccharide-induced acute lung injury by inhibiting the nuclear factor-kappaB signaling pathway. *Int Immunopharmacol.* 2013;16(4):475–480. Available at: http://doi.org/10.1016/j.intimp.2013.04.020
21. Zhong J, Wang Z, Xie Q, et al. Shikonin ameliorates D-galactose-induced oxidative stress and cognitive impairment in mice via the MAPK and nuclear factor-κB signaling pathway. *Int Immunopharmacol.* 2020;83:106491. Available at: http://doi.org/10.1016/j.intimp.2020.106491
22. Luo B, Ding X, Hu Y, et al. Shikonin hastens diabetic wound healing by inhibiting M1 macrophage polarisation through the MAPK signaling pathway. *Mol Immunol.* 2025;177:73–84. Available at: http://doi.org/10.1016/j.molimm.2024.12.002
23. Liu LL, Wu Y, Cao K, et al. Shikonin inhibits IFN-γ-induced K17 over-expression of HaCaT cells by interfering with STAT3 signaling. *Int J Clin Exp Pathol.* 2015;8(8):9202–9207.
24. Lan X, Wang H, Qi R, et al. Shikonin inhibits CEBPD downregulation in IL-17-treated HaCaT cells and in an imiquimod-induced psoriasis model. *Mol Med Rep.* 2020;22(3):2263–2272. Available at: http://doi.org/10.3892/mmr.2020.11315
25. Zhu ZJ, He LQ, Wang XD, et al. Research Progress of Chinese Medicine Monomer and Compound in the Treatment of Psoriasis by Regulating NF-κB Signaling Pathway. *Int J Adv Clin Sci Res.* 2024;3:21–32.
26. Zhou Y, Feng X, Xu H, et al. The application of natural product-delivering micro/nano systems in the treatment of inflammatory bowel disease. *J Mater Chem B.* 2023;11(2):244–260. Available at: http://doi.org/10.1039/D2TB01965E
27. Feng G, Zhang H, Liu H, et al. Natural Flavonoid-Derived Enzyme Mimics DHKNase Balance the Two-Edged Reactive Oxygen Species Function for Wound Healing and Inflammatory Bowel Disease Therapy. *Research (Wash D C).* 2024;7:0464. Available at: http://doi.org/10.34133/research.0464
28. Feng J, Wang Y, Lv Y, et al. XA pH-Responsive and Colitis-Targeted Nanoparticle Loaded with Shikonin for the Oral Treatment of Inflammatory Bowel Disease in Mice. *Mol Pharm.* 2022;19(11):4157–4170. Available at: http://doi.org/10.1021/acs.molpharmaceut.2c00550
29. Yao M, Ren M, Ding W, et al. Shikonin delivery nano system based on calcium alginate for targeted therapy of inflammatory bowel disease by modulating macrophage polarization. *J Drug*

Deliv Sci Technol. 2024;102:106336. Available at: http://doi.org/10.1016/j.jddst.2024.106336
30. Guo J, Miao Y, Nie F, et al. Zn-Shik-PEG nanoparticles alleviate inflammation and multi-organ damage in sepsis. *J Nanobiotechnology*. 2023;21(1):448. Available at: http://doi.org/10.1186/s12951-023-02224-3
31. Fu J, You L, Sun D, Zhang L, Zhao J, Li P. Shikonin-loaded PLGA nanoparticles: A promising strategy for psoriasis treatment. *Heliyon.* 2024;10(11):e31909. Available at: http://doi.org/10.1016/j.heliyon.2024.e31909
32. Xiang H, Xu S, Zhang W, Li Y, Zhou Y, Miao X. Skin permeation of curcumin nanocrystals: Effect of particle size, delivery vehicles, and permeation enhancer. *Colloids Surf B Biointerfaces.* 2023;224:113203. Available at: http://doi.org/10.1016/j.colsurfb.2023.113203
33. Lin X, Hu Y, Zhang C, et al. More severe toxicity of gold nanoparticles with rougher surface in mouse hippocampal neurons. *J Cent South Univ*. 2021;28(12):3642–3653. Available at: http://doi.org/10.1007/s11771-021-4844-1
34. Recio MC, Andujar I, Rios JL. Anti-inflammatory agents from plants: progress and potential. *Curr Med Chem.* 2012;19(14):2088–2103. Available at: http://doi.org/10.2174/092986712800229069
35. Sur S, Rathore A, Dave V, Reddy KR, Chouhan RS, Sadhu V. Recent developments in functionalized polymer nanoparticles for efficient drug delivery system. *Nano-Struct Nano-Objects.* 2019;20:100397. Available at: http://doi.org/10.1016/j.nanoso.2019.100397
36. Kolosionek TJ, Jiang RY, Meleis MM, Ebeling-Koning NE, Surmaitis RM. Polyethylene Glycol Misuse Causing Acute Renal Failure and Metabolic Acidosis Requiring Dialysis: A Case Report. *Cureus.* 2024;16(7):e65838. Available at: http://doi.org/10.7759/cureus.65838
37. Hu Y, Zeng G, Dong H, Yang D, Wang Y. Macrophage-membrane-camouflaged nanoagents for precise bacterial clearance. *Innovation.* 2025;6(7):100909. Available at: http://doi.org/10.1016/j.xinn.2025.100909
38. Zhou D, Zhuang R, Chang X, Li L. Enhanced Light-Harvesting Efficiency and Adaptation: A Review on Visible-Light-Driven Micro/Nanomotors. *Research (Wash D C)*. 2020;2020:6821595. Available at: http://doi.org/10.34133/2020/6821595
39. Xie LM, Liu JB, Yang Z, et al. Microrobotic Swarms for Cancer Therapy. *Research (Wash D C)*. 2025;8:0686. Available at: http://doi.org/10.34133/research.0686