Journal of Chemical Health Risks

www.jchr.org

JCHR (2025) 15(3), 1681-1695 | ISSN:2251-6727

Emerging Strategies in the Management of Ulcerative Colitis: A Review

Nidhi, Ramenani Hari Babu, Saurabh Sharma, Vijayshwari Mishra, Deepika Dawas

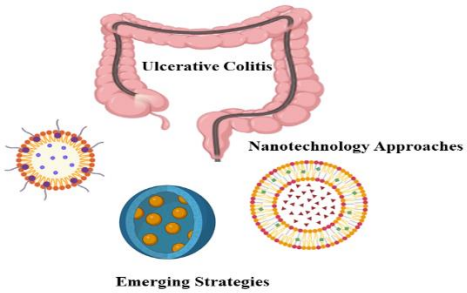
Teerthanker Mahaveer University Delhi Road, Nh 24, Bagadpur, Uttar Pradesh 244001.

(Received: 16 March 2025 Revised: 20 April 2025 Accepted: 01 May2025)

KEYWORDS

Ulcerative Colitis, inflammatory bowel disease, Acute Severe Ulcerative Colitis.

GRAPHICAL ABSTRACT:



Emerging Strategies in the Management of Ulcerative Colitis

ABSTRACT:

Ulcerative Colitis (UC) represents a critical and life-threatening. The rising incidence of UC, particularly in newly industrialized nations, coupled with limited access to advanced therapeutic options, underscores the pressing need for innovative strategies to manage Acute Severe Ulcerative Colitis (ASUC) effectively. ASUC necessitates hospitalization and intravenous corticosteroid therapy, which remains the cornerstone of treatment since its introduction in the 1950s. However, up to one-third of patients exhibit steroid refractoriness, requiring medical rescue therapies such as infliximab or cyclosporine or, in severe cases, surgical interventions like emergency colectomy. Recent advancements in biologic therapies and oral small molecules have revolutionized the treatment landscape for moderate to severe UC, but their application in ASUC remains limited. Current management strategies emphasize early identification of corticosteroid non-responders using clinical, biochemical, and endoscopic indices to facilitate timely escalation to rescue therapies. Despite these advances, a universally validated predictive index for corticosteroid or medical rescue therapy outcomes is lacking, necessitating further research to optimize treatment algorithms. Emerging evidence highlights the significant role of nutritional and dietary factors in modulating disease progression in UC. High-fat, high-sugar diets exacerbate mucosal dysbiosis and inflammatory signaling pathways, while fiber-rich diets that promote short-chain fatty acid (SCFA) production support mucosal barrier integrity and immune regulation. Deficiencies in micronutrients, including zinc, iron, and vitamin D, further compromise intestinal barrier function and exacerbate inflammation. The potential of dietary interventions to enhance remission induction and sustain remission in UC warrants comprehensive investigation. This review focuses on nanoformulation, and advancements in therapeutic options, and dietary factors in UC management. It underscores the importance of multidisciplinary approaches, integrating pharmacological innovations with nutritional strategies, to improve patient outcomes and reduce the burden of ASUC globally. Future research must prioritize the development of validated predictive tools and evidence-based dietary guidelines tailored to the unique needs of ASUC patients.

1. Introduction

Ulcerative colitis (UC) represents a distinct variant of inflammatory bowel disease (IBD) specifically confined to the large intestine, impacting approximately 5 million individuals worldwide, with a notable surge in incidence observed in developing nations [1]. Roughly 25% of individuals diagnosed with UC encounter profound exacerbations necessitating hospitalization and intravenous (IV) corticosteroids throughout the

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JCHR (2025) 15(3), 1681-1695 | ISSN:2251-6727

trajectory of their illness. With the advent of innovative treatments and the refinement of protocols, the frequency of hospitalizations linked to acute exacerbations appears to have diminished [2]. Nevertheless, in light of evolving epidemiological trends pertaining to UC, there has been an escalation in hospital admissions within newly industrialized nations [3]. More than one-third of individuals suffering from ASUC exhibit a lack of response to IV corticosteroids, necessitating the implementation of medical rescue therapies [4]. Currently, infliximab and cyclosporine are the sole agents that have undergone systematic evaluation and are endorsed as medical rescue therapies in cases of steroid-refractory ASUC. Prompt decision-making is critical, as undue delays in transitioning to surgical intervention in scenarios of medical therapy failure can result in heightened postoperative morbidity and mortality [5]. This highlights the necessity of reliably predicting the response to medical therapies at an early stage in the progression of ASUC to facilitate timely clinical decision-making. Regrettably, a single universally recognized index capable of accurately predicting responses to corticosteroid therapy remains elusive [6]. Continue to be the most frequently employed index for anticipating responses to corticosteroids. Although more contemporary indices have been developed in recent years, their operational characteristics have yet to be comprehensively validated, and no indices currently exist that can accurately forecast the failure of medical rescue therapy [7]. The complex processes through which nutritional elements influence UC remain partially elucidated. Regarding indirect influences, it has been posited that dietary-induced alterations in gut microbiota composition may play a role in the onset or persistence of inflammatory processes [8]. High-fat and/or high-sugar dietary patterns have been demonstrated to induce mucosal dysbiosis, which is characterized by an elevation in pro-inflammatory Proteobacteria and a reduction in anti-inflammatory bacterial populations. Furthermore, dietary intake can influence the metabolic activities of the microbiota [9]. Non-digestible fibers, are integral to preserving mucosal barrier integrity and regulating immune responses. Diets that are deficient in fiber and abundant in sugars and fats have been associated with diminished SCFA production, thereby increasing susceptibility to UC [10]. The direct impacts of dietary constituents on cellular functions have also been investigated. Prolonged consumption of diets high in fats or sugars may result in the excessive generation of free radicals [11]. This cascade leads to an augmented release of inflammatory cytokines and chemokines, which subsequently provokes a heightened immune response characterized by the mobilization of immune cells. Depletion of micronutrients, such as luminal iron deficiency, can exert direct effects on the functionality of intestinal epithelial cells and T cells [12]. A deficiency in zinc has been shown to compromise the integrity and permeability of the intestinal barrier. The role of vitamin D in enhancing the innate immune system and mitigating inflammation has been the subject of extensive study. Dietary consumption of arachidonic acid (an n-6 PUFA) has been linked to an increased likelihood of UC onset [13]. Western dietary pattern characterized by processed foods, saturated fats, sugars, red meats, and refined grains is associated with heightened mucosal inflammation [14]. Conversely, the ingestion of fruits and vegetables appears to mitigate the inflammatory risk associated with UC. Food additives such as maltodextrin and emulsifiers, along with thickening agents including carboxymethylcellulose, carrageenan, and xanthan gum, can also adversely affect intestinal homeostasis [15]. Despite the increasing number of reviews addressing the influence of dietary factors on the development of UC, the existing dietary guidelines for managing the condition remain limited and lack a solid scientific foundation. As a result, the inquiry arises as to whether dietary interventions can enhance the rates of remission induction or assist in sustaining remission among individuals afflicted with UC [16].

2. Pathophysiology of Ulcerative Colitis

Complex interplay of genetic, immunological, microbial, and environmental factors, which collectively drive an exaggerated immune response and profound mucosal damage [17]. At its core, ASUC is a disorder of immune dysregulation, marked by a breakdown in the intestinal epithelial barrier (figure 1), hyperactivation of innate and adaptive immune responses, and a persistent pro-inflammatory state [18]. Under normal conditions, the epithelial cells maintain tight junctions, producing mucins and antimicrobial peptides that prevent microbial invasion. However, in ASUC, there is a marked disruption of these tight junctions and epithelial integrity, leading to increased permeability [19]. This barrier

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JCHR (2025) 15(3), 1681-1695 | ISSN:2251-6727

dysfunction allows luminal antigens, including microbial products and dietary components, to translocate into the lamina propria, triggering an exaggerated immune response. This breach is further exacerbated by a deficiency in protective factors such as mucin 2 (MUC2) and trefoil factor family proteins, which normally aid in mucosal healing and protection [20]. Hyperactivated in ASUC due to the increased presence of microbial antigens. This activation leads to the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which amplify the inflammatory response [21]. These cytokines not only recruit neutrophils to the site of inflammation but also enhance their activation and lifespan, resulting in excessive neutrophil infiltration into the colonic mucosa. Neutrophils release reactive oxygen species (ROS), proteases, and neutrophil extracellular traps (NETs), contributing to tissue damage and perpetuating inflammation. The adaptive immune system also plays a central role in the pathophysiology of ASUC [22]. T-helper (Th) cell subsets, particularly Th1 and Th17 cells, are hyperactivated, resulting in an overproduction of cytokines such as interferon-gamma (IFN-γ) and interleukin-17 (IL-17). These cytokines further enhance the recruitment of inflammatory cells and promote a cycle of chronic inflammation and tissue injury. Regulatory T cells (Tregs), which normally suppress immune responses and maintain tolerance, are functionally impaired in ASUC, tipping the balance towards uncontrolled inflammation [23]. B cells and plasma cells also contribute to the inflammatory milieu by producing autoantibodies and activating complement pathways, leading to further tissue injury. The gut microbiota, which plays a vital role in maintaining intestinal homeostasis, is profoundly altered in ASUC. Dysbiosis, characterized by a reduction in beneficial bacteria such as Lactobacillus and Bifidobacterium and an increase in pathogenic bacteria such as Escherichia coli, is a hallmark of the disease. This microbial imbalance not only perpetuates barrier dysfunction but also amplifies the immune response [24]. Short-chain fatty acids (SCFAs), produced by the fermentation of dietary fibers by commensal bacteria, are significantly reduced in ASUC, leading to impaired epithelial repair and an enhanced inflammatory state. On a molecular level, ASUC is characterized by the activation of several key signaling pathways that drive inflammation and tissue damage. The nuclear factor-kappa B (NF-κB) pathway, a master regulator of inflammation, is persistently activated in epithelial and immune cells, leading to the production of a broad spectrum of inflammatory mediators. Similarly, the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is upregulated, particularly in response to cytokines such as IL-6 and IFN-γ, further amplifying the inflammatory response. Other pathways, such as the mitogen-activated protein kinase (MAPK) pathway and the inflammasome pathway, also contribute to the pathogenesis of ASUC by promoting cytokine release, apoptosis, and pyroptosis. Vascular changes and thrombosis are additional features of ASUC that contribute to its severity. Endothelial dysfunction and increased expression of adhesion molecules facilitate the recruitment of immune cells to the inflamed mucosa. Simultaneously, the hypercoagulable state observed in ASUC patients leads to microvascular thrombosis, ischemia, and further mucosal damage. These vascular abnormalities exacerbate the already impaired healing response and contribute to the development of complications such as toxic megacolon and perforation. The pathophysiology of ASUC also involves a dysregulated repair response. Inflammation-driven epithelial cell death, coupled with an impaired ability of stem cells in the intestinal crypts to regenerate the epithelium, results in persistent mucosal injury. This is compounded by the overexpression of matrix metalloproteinases (MMPs), which degrade extracellular matrix components and impede tissue repair. Angiogenesis, which is normally upregulated during healing, is paradoxically impaired in ASUC, further delaying mucosal recovery. Genetic and epigenetic factors play a contributory role in predisposing individuals to ASUC and modulating disease severity. Polymorphisms in genes involved in barrier function (e.g., MUC2), immune regulation (e.g., IL23R and TNFSF15), and microbial recognition (e.g., NOD2) have been implicated in increasing susceptibility to ASUC. Environmental factors, including diet, stress, and infections, act as triggers or exacerbating factors in ASUC. High-fat diets, smoking cessation, and certain medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) have been linked to disease flares [25].

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JCHR (2025) 15(3), 1681-1695 | ISSN:2251-6727

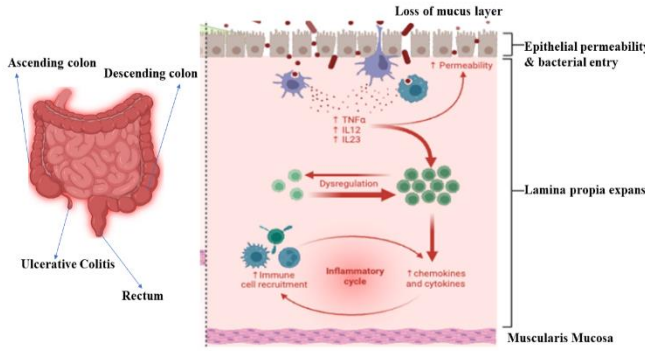

Figure 1: Pathophysiology of Ulcerative Colitis

3. Role of Gut Microbiota in Ulcerative Colitis

The gut microbiota plays a central role in the pathogenesis and progression of UC (figure 2). Comprising trillions of microorganisms, including bacteria, fungi, viruses, and archaea, the gut microbiota is integral to maintaining intestinal homeostasis, regulating immune responses, and protecting the epithelial barrier [26]. Dysbiosis involves a reduction in microbial diversity, a depletion of beneficial commensal bacteria, and an overrepresentation of potentially pathogenic species. The alterations in microbial composition and function contribute significantly to the onset, perpetuation, and exacerbation of colonic inflammation, as well as the mucosal injury observed in UC [27]. Under normal physiological conditions, the gut microbiota contributes to intestinal health by promoting immune tolerance, regulating inflammation, and producing metabolites essential for epithelial integrity and repair [28]. Beneficial bacterial species, such as Bifidobacterium and Lactobacillus, produce short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate, through the fermentation of dietary fibers. SCFAs serve as critical energy sources for colonocytes and promote anti-inflammatory effects by inhibiting histone deacetylases, activating G-protein-coupled receptors (e.g., GPR43), and modulating regulatory T cell (Treg) function. However, in UC, dysbiosis leads to a substantial reduction in SCFA-producing bacteria, resulting in diminished butyrate levels and impaired epithelial energy metabolism [29]. The lack of SCFAs contributes to a breakdown of the intestinal epithelial barrier, increased permeability, and heightened exposure of the immune system to luminal antigens, thereby driving inflammation [30]. Dysbiosis in UC is characterized by an overgrowth of pro-inflammatory and mucolytic bacteria, such as Escherichia coli, Enterococcus faecalis, and Fusobacterium nucleatum, and a reduction in anti-inflammatory species like Faecalibacterium prausnitzii and Roseburia [31]. Pathogenic species secrete toxins, proteases, and inflammatory mediators that directly damage the epithelial barrier and stimulate immune responses. For instance, adherent-invasive Escherichia coli (AIEC) strains are frequently identified in UC patients and exhibit the ability to adhere to and invade epithelial cells [32], induce the release of inflammatory cytokines such as interleukin-8 (IL-8), and activate macrophages. This leads to a pro-inflammatory cascade that perpetuates mucosal injury. Furthermore, Fusobacterium nucleatum, known for its virulence in colorectal cancer, has been implicated in UC due to its ability to invade epithelial cells and stimulate neutrophil recruitment, contributing to localized inflammation [33]. The altered microbial community in UC also leads to a shift in metabolic outputs, which impacts the host's immune and metabolic environment. Beyond the reduction of SCFAs, there is an increase in harmful metabolites such as hydrogen sulfide, ammonia, and lipopolysaccharides (LPS) [34]. Hydrogen sulfide, produced by sulfate-reducing bacteria like desulfovibrio, impairs mitochondrial function and inhibits butyrate oxidation in colonocytes, further disrupting energy metabolism and barrier integrity. Similarly, LPS derived from gram-negative bacteria activates Toll-like receptor 4 (TLR4) signaling, driving the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6) [35]. These cytokines amplify inflammation and contribute to immune cell recruitment and activation in the colonic mucosa. The gut microbiota also influences the function of the innate and adaptive immune systems, which are dysregulated in UC. Commensal bacteria under normal conditions promote immune tolerance [36]. This interaction triggers anti-inflammatory pathways and fosters the development of Tregs, which secrete interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) to suppress inflammation. However, in UC, dysbiosis results in the hyperactivation of PRRs due to the increased presence of microbial antigens and pathogenic bacteria. This leads to excessive activation of innate immune cells such as macrophages and dendritic cells, which release pro-

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JCHR (2025) 15(3), 1681-1695 | ISSN:2251-6727

inflammatory mediators, driving a Th1 and Th17 immune response. Th17 cells, in particular, produce interleukin-17 (IL-17), which exacerbate epithelial injury and inflammation [37]. Another crucial aspect of microbiota-host interaction in UC is the impaired ability of the gut microbiota to regulate the mucosal barrier and epithelial repair processes. Commensal bacteria and their metabolites typically promote the production of mucins and antimicrobial peptides, such as defensins, that protect the mucosal surface from microbial invasion. Dysbiosis in UC is associated with a decrease in these protective factors, making the epithelium more susceptible to invasion by pathogenic bacteria. Additionally, the overexpression of mucolytic bacteria like Akkermansia muciniphila and Ruminococcus gnavus leads to the degradation of the mucus layer, further compromising barrier function and allowing greater microbial translocation into the lamina propria. This results in a vicious cycle of barrier dysfunction and immune activation, perpetuating the inflammatory process. The role of gut microbiota in UC extends beyond local inflammation to systemic effects on the host. Dysbiosis and increased intestinal permeability in UC patients are linked to the translocation of microbial products into the systemic circulation, a phenomenon referred to as "microbial translocation." This systemic exposure to microbial antigens can lead to low-grade systemic inflammation and contribute to extraintestinal manifestations of UC, such as arthritis, uveitis, and primary sclerosing cholangitis. Moreover, the chronic inflammatory state driven by dysbiosis is associated with an increased risk of colorectal cancer in UC patients [38]. Emerging evidence also highlights the role of microbial biofilms in UC pathogenesis. Biofilms, which are dense aggregates of microorganisms encased in an extracellular matrix, are increasingly recognized as a feature of the dysbiotic microbiota in UC. Pathogenic biofilms, predominantly composed of mucolytic and pro-inflammatory bacteria, adhere to the colonic mucosa and resist clearance by the immune system and antimicrobial agents [39]. These biofilms disrupt the spatial segregation between the microbiota and the epithelial surface, exacerbating immune activation and barrier dysfunction. Therapeutic strategies targeting the gut microbiota are gaining prominence in UC management, aiming to restore microbial balance and ameliorate inflammation. Probiotics, such as Bifidobacterium and Lactobacillus species, have shown promise in clinical trials by modulating immune responses and enhancing barrier function. Similarly, prebiotics like fructooligosaccharides and inulin support the growth of beneficial bacteria and the production of SCFAs. Fecal microbiota transplantation (FMT) has emerged as a novel approach for treating dysbiosis in UC, with studies demonstrating its potential to induce remission by reconstituting a healthy microbial community [40]. However, the variability in FMT outcomes underscores the need for a better understanding of the donor microbiota and host-microbiota interactions. Traditional interventions, dietary modifications are being explored to modulate the gut microbiota in UC. Diets rich in fermentable fibers, polyphenols, and omega-3 fatty acids support the growth of beneficial bacteria and the production of anti-inflammatory metabolites. Conversely, diets high in saturated fats, red meat, and processed foods are associated with dysbiosis and an increased risk of UC flares [41]. Targeted dietary interventions, tailored to individual microbiota profiles, may offer a personalized approach to managing UC. Advances in metagenomics, metabolomics, and other omics technologies have provided new insights into the role of the gut microbiota in UC and the identification of potential therapeutic targets. For instance, specific microbial signatures, such as the abundance of Faecalibacterium prausnitzii and the ratio of Firmicutes to Bacteroidetes, are being investigated as biomarkers for disease activity and treatment response. Similarly, microbial metabolites, including SCFAs and bile acids, are being explored as therapeutic agents to restore mucosal homeostasis [42].

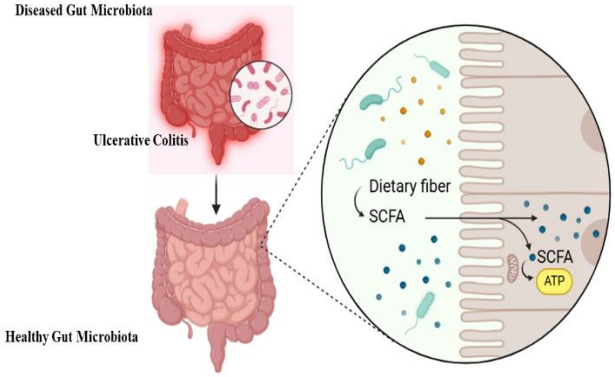

Figure 2: Role of Gut Microbiota in Ulcerative Colitis

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JCHR (2025) 15(3), 1681-1695 | ISSN:2251-6727

4. Nanotherapies therapy for Ulcerative Colitis Management

Despite the availability of conventional therapies such as corticosteroids, immunosuppressive drugs, and biologics, many patients experience inadequate responses or undesirable side effects. Thus, there is a growing need for innovative treatment strategies that can enhance the therapeutic outcomes for UC patients while minimizing adverse effects [43]. One promising approach to addressing these challenges is the use of nanotherapy, which leverages nanotechnology to deliver drugs more efficiently, with enhanced precision and controlled release [44]. Nanotherapy is rapidly evolving, offering novel solutions to overcome the limitations of traditional treatments by improving the bioavailability, stability, and targeting of therapeutic agents. Nanoparticle-based drug delivery systems have been identified as an essential component of emerging therapies, allowing for the encapsulation of active pharmaceutical ingredients in nanocarriers, such as liposomes, dendrimers, nanoparticles, and micelles [45]. These carriers enhance the solubility and bioavailability of poorly soluble drugs, provide controlled release of active substances, and enable targeted delivery to specific sites of inflammation in the colon. One of the most widely explored forms of nanotherapy for UC involves the use of liposomal formulations [46]. Liposomes are spherical vesicles composed of lipid bilayers that can encapsulate a wide range of therapeutic agents, including corticosteroids, immunomodulatory drugs, and biologics, thus enhancing their stability, extending their half-life, and ensuring their efficient delivery to the site of action [47]. Liposomes can be engineered to respond to the pH and other physiological conditions in the gastrointestinal tract, ensuring that the drug is released in the inflamed mucosa, which is typical in UC patients. Moreover, liposomes can be surface-modified with targeting ligands that bind to receptors present on the inflamed tissues, further enhancing the precision of drug delivery. Another emerging class of nanotherapeutic agents for UC is polymeric nanoparticles [48]. These nanoparticles are made of biodegradable polymers that can encapsulate both hydrophilic and hydrophobic drugs, providing an efficient means of delivering poorly water-soluble drugs that are otherwise difficult to administer [49]. Polymeric nanoparticles offer sustained-release properties, reducing the frequency of dosing and maintaining therapeutic drug concentrations for extended periods [50]. These nanoparticles can be designed to protect encapsulated drugs from degradation, such as the degradation caused by digestive enzymes in the gastrointestinal tract [51]. The surface of these nanoparticles can also be functionalized with ligands that specifically target inflammatory cells or the gut epithelial cells, further improving the precision of drug delivery. Solid lipid nanoparticles (SLNs) are another promising class of nanocarriers that can be used to deliver therapeutic agents to UC patients [52]. SLNs are solid at body temperature and can encapsulate both lipophilic and hydrophilic drugs. These nanoparticles offer several advantages, including controlled drug release, reduced drug toxicity, and enhanced drug bioavailability [53]. SLNs are particularly advantageous in treating UC because they can provide a sustained release of anti-inflammatory drugs, reducing the need for frequent dosing and providing longer-lasting effects. Additionally, nanogels, which are hydrophilic, cross-linked polymeric networks, are increasingly being investigated for UC treatment [54]. These nanogels can encapsulate therapeutic agents and respond to stimuli such as pH, temperature, or ionic strength, making them ideal for targeted drug delivery. In UC, nanogels can be engineered to release their payloads in response to the acidic environment present in the inflamed regions of the colon, ensuring that the drug is delivered precisely where it is needed [55]. Dendrimers are another class of nanocarriers that show promise in UC treatment. These are branched, tree-like macromolecules that provide a high degree of surface functionality, allowing for the attachment of drugs, targeting ligands, or imaging agents. Dendrimers can deliver drugs in a controlled manner and offer the advantage of being able to cross the intestinal barrier [56], facilitating the efficient delivery of therapeutic agents to the site of inflammation in the colon. Furthermore, micelles, which are self-assembled structures composed of amphiphilic molecules, can be used to deliver hydrophobic drugs and improve their solubility. These nanoparticles are small enough to penetrate the mucosal barrier and can deliver encapsulated drugs directly to the inflamed tissue in UC [57]. Micelles also offer the advantage of reducing the toxicity associated with the systemic distribution of drugs by concentrating their effects at the disease site

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[58]. Another emerging strategy is the use of carbon-based nanomaterials, such as carbon nanotubes and carbon quantum dots, which have unique properties that make them ideal for drug delivery in UC. Carbon nanotubes, for instance, can carry a large payload of drugs and penetrate the intestinal mucosa, reaching the inflamed regions of the colon. Carbon quantum dots, with their fluorescent properties, can also serve as both diagnostic and therapeutic agents, offering an innovative approach to the treatment and monitoring of UC [59]. Exosome-based drug delivery is a novel strategy that is gaining attention for UC treatment. Exosomes are small, naturally occurring vesicles that can carry and deliver therapeutic molecules, including RNA, proteins, and drugs. Exosome-based therapies exploit the body's own machinery for drug delivery, offering a biocompatible and non-immunogenic alternative to synthetic nanoparticles. Exosomes can be engineered to encapsulate drugs that target specific inflammatory pathways in UC and can be surface-modified to enhance their targeting capabilities [60]. Moreover, exosomes can be used for gene delivery, allowing for the modulation of gene expression in UC patients, which can help to reduce inflammation and promote healing. RNA-based nanomedicines also represent an exciting frontier in the management of UC. RNA therapeutics, such as small interfering RNA (siRNA) or messenger RNA (mRNA), can be delivered to the inflamed tissues using nanoparticles, where they can modulate gene expression and suppress the inflammatory pathways that drive UC [61]. siRNA, for example, can silence pro-inflammatory genes, while mRNA can be used to deliver therapeutic proteins directly to the inflamed tissues. Nanoparticles can protect these RNA molecules from degradation and facilitate their targeted delivery, making RNA-based therapies a promising tool in the treatment of UC. Nanostructured lipid carriers (NLCs), which combine the advantages of solid lipid nanoparticles and liquid lipid carriers, are increasingly being explored for UC treatment. NLCs are highly stable, have a high drug loading capacity, and can provide sustained release of therapeutic agents, making them ideal for delivering anti-inflammatory drugs to the inflamed tissues of the colon [62]. As UC treatment continues to evolve, biodegradable nanoparticles and stimuli-responsive nanomaterials are gaining traction for their ability to deliver drugs in a controlled manner. Stimuli-responsive nanomaterials, for example, can release their payload in response to specific triggers, such as changes in pH or enzymatic activity, allowing for highly targeted drug delivery to the inflamed regions of the colon [63]. The ability to modulate drug release in response to the changing conditions in the gut presents a significant advantage in managing UC, where localized drug delivery can minimize side effects and maximize therapeutic effects. The development of these emerging nanotherapies for UC is expected to lead to more effective, safer, and personalized treatment options. However, despite the promising potential of nanotechnology, challenges remain in translating these therapies into clinical practice. Issues such as the scalability of production, long-term safety, and the cost-effectiveness of nanotherapies must be addressed before they can become a mainstay in UC management [64]. Inflammatory bowel disease (IBD) constitutes a significant global health concern, with North America, particularly the United States, playing an influential role in the global prevalence of IBD patients. Topical corticosteroids, such as enema formulations containing micronized budesonide, represent a viable therapeutic option for distal colitis [65]. Nevertheless, assert that the particle size may be excessive for effective penetration of colonic mucus and recommend the utilization of budesonide nanosuspension (NS) with optimized coating and dimensions to facilitate enhanced permeation. Their investigation demonstrated that muco-inert fluorescent polystyrene particles of 200 nm in diameter, coated with Pluronic F127, exhibited superior mucus penetration in a murine model. A rat model of colitis was established via the administration of TNBS. The diffusion characteristics of the nanoparticles revealed an average size of 110.5 nm [66]. Lyophilized probiotic extract encapsulated in PLGA (poly(lactic-co-glycolic acid)) nanoparticles has emerged as a promising strategy for targeted drug delivery and enhanced therapeutic efficacy, particularly in the treatment of gastrointestinal disorders [67]. Probiotics, live microorganisms that confer health benefits to the host when administered in adequate amounts, are well known for their anti-inflammatory, antioxidant, and gut microbiota-modulating properties. However, the therapeutic potential of probiotics is often limited by their instability under physiological conditions, short gastrointestinal transit time, and reduced viability due to the harsh acidic environment in

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the stomach and enzymatic degradation in the intestine [68]. To overcome these limitations, the encapsulation of lyophilized probiotic extracts within biodegradable and biocompatible PLGA nanoparticles has been developed as an innovative approach. PLGA nanoparticles protect the probiotics from degradation, ensuring prolonged stability and controlled release at the target site in the colon. Lyophilization (freeze-drying) of probiotic extracts is a critical step that ensures the long-term preservation of the bioactive components without compromising their functional activity [69]. When combined with PLGA nanoparticles, the lyophilized probiotic extracts achieve enhanced bioavailability and targeted delivery, as PLGA's polymeric structure can be designed to respond to pH variations in the gastrointestinal tract. In this regard, PLGA nanoparticles have shown significant advantages, such as enhanced encapsulation efficiency, reduced burst release, and tunable degradation rates, which enable a sustained and localized release of the probiotic components in the colon, where their therapeutic action is most needed. The size, surface charge, and hydrophobicity of the PLGA nanoparticles can be optimized to ensure effective mucosal adhesion, cellular uptake, and penetration across intestinal barriers. The encapsulation process also shields the probiotic bioactive components from premature degradation caused by gastric acid, bile salts, and digestive enzymes. This protective mechanism ensures higher probiotic viability and activity upon reaching the colon. The controlled release profile of PLGA nanoparticles reduces the need for frequent dosing, enhancing patient compliance and therapeutic outcomes. Overall, the encapsulation of lyophilized probiotic extracts in PLGA nanoparticles represents a cutting-edge nanotechnology-based approach for improving probiotic delivery, enhancing their therapeutic potential, and addressing the challenges associated with gastrointestinal diseases [70].

Table 1: Nanoformulations for UC Management

Phytochemicals	**Nanoformulations**	***In-Vivo* models**	**References**
Resveratrol	CTS-NPs	*In-vitro*	[71]
Curcumin	PEG	DSS	[72]
Curcumin	C-SBLNPs	DSS	[73]
Silymarin	Selenium NPs and Eudragit NPs	TNBS and AA	[74]
NF-kB decoy oligonucleotide	CTS-PLGA NSs	DSS	[75]
Quercetin	PEG-coated vesicles with CTS	TNBS	[76]
Grape Exosome	GELNPs and LLNs	DSS	[77]
Caffeic acid phenethyl ester (CAPE)	Albumin	DSS	[78]
Probiotic derived protein p40	Pectin/Zein Hydrogel	*In-vitro, ex-vivo*, and DSS	[79]
α4β7 integrin	SLKs	DSS	[80]
Colonic bacteria	ZnO NPs	DSS	[81]
MAPK4 siRNA	β1,3-D-glucan shells	LPSS	[82]
IL-10 RNA	LNPs	*In-vivo*	[83]
Tuftsin	Phosphocholine	DSS	[84]

Conclusion

Despite the availability of conventional therapies such as corticosteroids, immunosuppressive drugs, and biologics, the management of UC remains challenging due to the high incidence of inadequate responses, adverse effects, and disease relapse. Therefore, the growing demand for innovative treatment strategies has led to the exploration of nanotherapies, which leverage nanotechnology to deliver therapeutic agents with enhanced precision, bioavailability, and controlled release. Nanotherapies offer a significant advancement in UC management by overcoming the limitations of traditional treatments, such as systemic toxicity, rapid drug clearance, and lack of targeted delivery. Among the most widely explored nanocarriers are liposomes, polymeric nanoparticles, SLNs, dendrimers, micelles, nanogels, carbon-based nanomaterials, and exosome-based drug delivery systems. Each of these systems brings unique advantages that make them promising

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candidates for addressing the challenges associated with UC treatment. Liposomes, spherical vesicles composed of lipid bilayers, are at the forefront of nanotherapeutic approaches for UC. Their ability to encapsulate a wide range of therapeutic agents, such as corticosteroids, immunomodulators, and biologics, enhances drug stability, prolongs circulation time, and ensures precise delivery to inflamed tissues. Liposomal formulations can be engineered to respond to pH changes in the gastrointestinal tract, allowing for site-specific drug release in the inflamed mucosa. Composed of biocompatible and biodegradable polymers such as PLGA, these nanoparticles can encapsulate both hydrophilic and hydrophobic drugs, making them ideal for delivering poorly water-soluble therapeutic agents. Polymeric nanoparticles offer controlled and sustained drug release, which reduces the frequency of dosing and ensures prolonged therapeutic effects. Surface functionalization with targeting moieties, such as antibodies or peptides, enhances the nanoparticles' ability to deliver drugs directly to inflammatory cells or gut epithelial tissues, minimizing off-target effects and systemic toxicity. Dendrimers, highly branched macromolecules with a well-defined architecture, have emerged as versatile nanocarriers for UC therapy. Their unique structure allows for the attachment of multiple therapeutic agents, targeting ligands, or imaging molecules on their surface. Dendrimers facilitate controlled drug release and possess the ability to cross biological barriers, such as the intestinal epithelium, enabling efficient drug delivery to inflamed regions in the colon. Furthermore, dendrimers can be functionalized to target specific inflammatory pathways, providing a more focused therapeutic approach to UC. Nanogels, which are hydrophilic and cross-linked polymeric networks, have also shown potential for UC treatment. These nanocarriers can encapsulate therapeutic agents and release them in response to specific physiological stimuli, such as pH, temperature, or ionic strength. In UC, nanogels can be engineered to release their payloads in the acidic environment of inflamed colonic tissues, ensuring precise and targeted drug delivery. The tunable properties of nanogels make them ideal for delivering anti-inflammatory agents or biologics with enhanced efficacy and minimal off-target effects. Micelles, self-assembled structures formed by amphiphilic molecules, are another class of nanocarriers that hold promise for UC therapy. Micelles can encapsulate poorly water-soluble drugs, enhancing their solubility and bioavailability. Their small size enables them to penetrate the mucosal barrier and deliver encapsulated drugs directly to the inflamed tissues. These multifunctional nanomaterials offer innovative solutions for the treatment and monitoring of UC, providing a promising platform for theragnostic applications. Exosome-based drug delivery systems represent a novel and biocompatible approach to UC management. Exosomes, naturally occurring extracellular vesicles, can carry a variety of therapeutic molecules, including proteins, RNA, and small molecules. Exosomes are non-immunogenic and can be engineered to target specific inflammatory pathways in UC. They can also be surface-modified to enhance their targeting capabilities, enabling the delivery of drugs or gene therapies to inflamed tissues with high precision. Exosome-based therapies hold significant potential for modulating gene expression, reducing inflammation, and promoting tissue repair in UC patients. RNA-based nanomedicines, including siRNA and miRNA therapies, are also emerging as powerful tools for UC management. These therapies involve the delivery of RNA molecules that target specific inflammatory pathways or gene expressions associated with UC pathogenesis. Nanocarriers such as lipid nanoparticles or polymeric nanoparticles are used to protect RNA molecules from degradation and facilitate their delivery to target cells. RNA-based therapies offer a highly specific and targeted approach to modulating the immune response and reducing inflammation in UC patients. In conclusion, while conventional therapies remain the mainstay of UC management, their limitations have paved the way for innovative strategies such as nanotherapy, which offer improved precision, bioavailability, and therapeutic outcomes.

Abbreviations

ASUC - Acute Severe Ulcerative Colitis

UC - Ulcerative Colitis

SLNs - Solid Lipid Nanoparticles

NPs - Nanoparticles

RNA - Ribonucleic Acid

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PLGA - Poly(lactic-co-glycolic acid)

DDS - Drug Delivery Systems

TNF-α - Tumor Necrosis Factor-alpha

NF-κB - Nuclear Factor kappa B

PEG - Polyethylene Glycol

pH - Potential of Hydrogen (acid-base balance)

IL - Interleukin

CD - Cluster of Differentiation

DSS - Dextran Sodium Sulfate

AOM - Azoxymethane

mRNA - Messenger Ribonucleic Acid

SLKs - Sphingomyelin-based Lipid Nanocarriers

CTS - Chitosan

NF-κB - Nuclear Factor kappa-light-chain-enhancer of activated B cells

MAPK - Mitogen-Activated Protein Kinase

siRNA - Small Interfering Ribonucleic Acid

IL-10 - Interleukin-10

β1,3-D-glucan - Beta-1,3-D-glucan

eGFP - Enhanced Green Fluorescent Protein

DTSSP - Dithiobis(succinimidyl propionate)

Acknowledgments

The authors would like to thank the College of Pharmacy and Teerthanker Mahaveer University, for their support and encouragement.

Author Contributions

Conceptualization: RHB and SS; Investigation, writing—original draft preparation: N; Writing—review and editing: VM and DD. All authors have read and agreed to the manuscript.

Funding

Not applicable

Data availability

All data obtained during this study are included in this manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

The work described has not been submitted elsewhere for publication, in whole or in part, and all authors participated in the work and have agreed to the content of the manuscript.

Competing interests

The authors declare that they have no known competing financial interests or personal relationships that could influence the work reported in this study.

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