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Integrative Therapeutic Strategies for Ulcerative Colitis: From Phytotherapy to Advanced Non-Herbal Novel Drug Delivery Systems and Formulations

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ABSTRACT:

Ulcerative colitis (UC) is a chronic, relapsing inflammatory bowel disease characterized by continuous mucosal inflammation of the colon and rectum. Conventional pharmacotherapies, including aminosalicylates, corticosteroids, immunomodulators, and biologics, frequently fail to sustain long-term remission and are associated with dose-limiting toxicities, secondary non-response, and high economic burden. In response, phytotherapy has emerged as a compelling multi-target therapeutic strategy, leveraging the anti-inflammatory, antioxidant, immunomodulatory, and microbiota-modulating properties of plant-derived bioactive compounds. However, clinical translation is constrained by poor aqueous solubility, rapid hepatic clearance, batch-to-batch phytochemical variability, and inadequate standardization. This review critically presents recent advances in integrative therapeutic strategies for UC, spanning traditional phytotherapeutics to advanced non-herbal novel drug delivery systems (NDDS). We examine mechanistic insights of herbal interventions, pharmacokinetic limitations of conventional botanicals, and the rational design of nanocarriers, vesicular platforms, targeted colon delivery systems, stimuli-responsive hydrogels, and RNA-based therapeutics. Special emphasis is placed on hybrid phyto-non-herbal formulations that synergistically enhance mucosal targeting, therapeutic efficacy, and safety profiles. Preclinical and emerging clinical evidence, alongside regulatory frameworks and quality control considerations, are systematically evaluated to delineate translational pathways. Current data underscore the potential of engineered delivery systems to overcome pharmacokinetic barriers, modulate the gut microbiome, and enable precision mucosal healing. Despite promising outcomes, challenges in clinical trial design, long-term safety assessment, and regulatory harmonization persist. Future research must prioritize multicenter randomized trials, pharmacogenomic profiling, and AI-driven formulation optimization to realize the full clinical potential of integrative UC therapeutics.

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INTRODUCTION:

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease (IBD) characterized by diffuse, continuous mucosal and submucosal inflammation extending proximally from the rectum [1]. The global prevalence of UC is rising, with epidemiological transitions paralleling urbanization, dietary westernization, and environmental shifts, particularly across Asia, South America, and the Middle East [2]. The pathophysiology of UC is multifactorial, involving complex crosstalk among genetic susceptibility, dysregulated mucosal immunity, environmental triggers, and profound gut microbiota dysbiosis [3]. Clinically, UC manifests with bloody diarrhea, abdominal pain, urgency, and systemic complications, significantly impairing quality of life and elevating the long-term risk of colorectal carcinoma [4].

Current pharmacological management relies on a step-up approach incorporating 5-aminosalicylates (5-ASAs), corticosteroids, immunomodulators, and biologic agents targeting specific inflammatory cytokines or integrins [5]. While these therapies can induce remission, their utility is constrained by dose-limiting toxicities, secondary non-response, high treatment costs, and increased infection risks [6]. Corticosteroids, though highly effective for acute flares, are unsuitable for maintenance therapy due to metabolic disturbances, osteoporosis, and hypertension. Moreover, approximately 30–40% of patients exhibit primary non-response or lose response to biologics over time, underscoring the urgent need for safer, more efficacious alternatives [7].

In this context, phytotherapy has garnered renewed scientific interest as a multi-target therapeutic modality. Plant-derived bioactive compounds—including curcuminoids, flavonoids, alkaloids, and terpenoids—exert pleiotropic effects by modulating NF-κB/MAPK signaling, restoring redox homeostasis via Nrf2 activation, rebalancing Th17/Treg immunity, and remodeling the gut microbiome toward a eubiotic state [8–11]. Traditional systems such as Ayurveda and Traditional Chinese Medicine (TCM) have utilized these botanicals for centuries, and contemporary studies consistently validate their mucosal healing and anti-inflammatory potential [12]. However, the clinical translation of herbal interventions is impeded by inherent pharmacokinetic limitations, including poor aqueous solubility, rapid phase I/II metabolism, efflux transporter susceptibility, and subtherapeutic colonic tissue concentrations. Additionally, batch-to-batch phytochemical variability, lack of standardized dosing, and insufficient rigorous clinical trial design hinder regulatory approval and mainstream adoption [13].

To overcome these barriers, advanced non-herbal novel drug delivery systems (NDDS) have been engineered to enhance site-specific targeting, prolong mucosal residence, protect labile compounds from degradation, and enable controlled release in the inflamed colon [14]. Nanocarriers, vesicular platforms, stimuli-responsive hydrogels, and microbiota-triggered systems represent a paradigm shift in UC therapeutics, offering precision delivery of both synthetic and botanical payloads [15]. Furthermore, hybrid formulations that integrate phytochemicals with nanomaterials or conventional drugs demonstrate synergistic efficacy, reduced toxicity, and multi-axis pathway modulation [16].

This review provides a comprehensive appraisal of integrative therapeutic strategies for UC, spanning traditional phytotherapeutics to cutting-edge NDDS. We critically evaluate mechanistic insights, preclinical and clinical evidence, safety profiles, and regulatory considerations, while highlighting current limitations and future research directions. By bridging ethnopharmacological knowledge with modern pharmaceutical engineering, this article aims to guide clinicians, researchers, and regulatory stakeholders toward the rational development of next-generation UC therapies.

2. Historical and Traditional Use of Herbal Remedies for UC:

2.1 Ethnobotanical Perspectives on UC Treatment

Herbal remedies have been an important part for UC management over various cultures since centuries. Ethnobotanical evidence indicates that more than 80% of the world's population use traditional medicine, most probably plant-based therapies for chronic diseases such as UC because they are available and affordable and perceived safer than conventional drugs [17]. Herbal medicine in China has been used for thousands of years to treat UC, and traditional Chinese literature recorded its use for intestinal diseases. Their multi-targeted effects, including anti-inflammatory, antioxidant and immune-modulating properties are the mechanisms responsible for these remedies [18]. Herbal plants are the basis of many indigenous health care systems, especially in countries such as India, Ethiopia, and Central and South America where they are abundant and low cost. Herbal remedies seek to revive intestinal balance, promote mucosal healing, and reduce inflammation, thereby relieving the hallmark symptoms of UC, including diarrhea, abdominal pain, and rectal bleeding. A survey among the

Zeliangrong people of northeastern India for ethnodrug plants used against stomach complaints maybe an equivalent to UC in terms of gut inflammation [19]. African sub-continent has employed plant sources like *Ximenia americana* for curing gastrointestinal inflammations. The extracts (or tea) from the bark have been demonstrated to decrease inflammation by suppression of neutrophil function. In the herbal medicine of several aboriginal groups in Australia and Indigenous peoples of the Americas, aloe was used to treat stomach disorders, inflammations, constipation, infections in the abdomen or colon [20].

2.2 Traditional Medicine Approaches for Managing UC:

Traditional Chinese Medicine (TCM) is the most well-documented system to treat UC. TCM treats AC by syndrome differentiation and matching herbal formulas to specific presentations such as damp-heat in the large intestine, or spleen deficiency [21,22]. TCM is a hopeful therapy for UC because of its significant effect, low recurrence and few side effects. Therapies may include single herbs, complex concoctions, or specific procedures such as herbal-retention enemas that administer decoctions directly to the colon for greater potency and minimal systemic side effects. TCM treatments are designed to adjust abnormal gut microbiota, immune response and the integrity of the intestinal barrier in order to re-establish intestinal homeostasis [23,24]. However, the use of herbal preparations for UC in other forms of traditional medicine such as Ayurveda and folk remedies is less documented [25]. List of plants used in traditional herbal formulations to treat UC is mentioned in Table 1.

Table 1: Phytochemical profile and pharmacological mechanisms of herbal formulations in the treatment of UC.

S no.	Plant source	Bioactive compound	Traditional use	Herbal formulation/ Extract	Mechanism of action	References
1.	*Curcuma longa*	Curcumin	Anti-inflammatory, gut healing	Extract, powder, decoction	Inhibits NF-κB, reduces cytokines, antioxidant, modulates gut flora	[26]
2.	*Boswellia serrata*	Boswellic acid	Anti-inflammatory, pain relief	Resin extract	Inhibits 5-LOX, reduces leukotrienes, anti-inflammatory	[27]
3.	*Glycyrrhiza glabra*	Glycyrrhizin, flavonoids	Mucosal healing, anti-ulcer	Decoction, extract	Antioxidant, modulates cytokines, supports mucosal barrier	[28]
4.	*Aloe vera*	Aloe polysaccharides, aloein	Mucosal repair, anti-ulcer	Gel, extract	Anti-inflammatory, promotes epithelial repair, modulates immune response	[29]
5.	*Andrographis paniculata*	Andrographolide	Anti-inflammatory	Extract, capsule	Inhibits NF-κB, reduces cytokines, antioxidant	[30]
6.	*Camellia sinensis*	Catechins	Antioxidant, anti-inflammatory	Tea, extract	Antioxidant, modulates inflammatory pathways	[31]
7.	*Zingiber officinale*	Shogaol, gingerol	Anti-inflammatory, gut health	Extract, powder	Inhibits COX/LOX, antioxidant, reduces cytokines	[32]
8.	*Arctium lappa*	Arctigenin	Anti-inflammatory	Extract	Antioxidant, modulates immune response	[33]
9.	*Plantago major*	Polysaccharides, aucubin	Mucosal healing	Extract, decoction	Anti-inflammatory, supports mucosal barrier	[34]
10.	*Punica granatum*	Ellagitannins, punicalagin	Antioxidant, anti-ulcer	Juice, extract	Antioxidant, reduces inflammation	[35]
11.	*Triticum aestivum*	Chlorophyll, flavonoids	Mucosal healing, anti-ulcer	Juice, extract	Antioxidant, supports mucosal repair	[36]
12.	*Scutellaria baicalensis*	Baicalin, wogonin	Heat-clearing, anti-inflammatory	Decoction, extract	Inhibits NF-κB, antioxidant, modulates gut flora	[37]
13.	*Paeonia lactiflora*	Paeoniflorin	Dampness-heat clearing	Decoction, extract	Anti-inflammatory, modulates immune response	[38]
14.	*Coptis chinensis*	Berberine	Heat-clearing, anti-ulcer	Decoction, extract	Inhibits NF-κB, modulates gut microbiota	[39]
15.	*Atractylodes macrocephala*	Polysaccharides	Spleen strengthening	Decoction, extract	Modulates immune response, supports gut barrier	[40]
16.	*Poria cocos*	Polysaccharides	Dampness-draining	Decoction, extract	Immunomodulatory, supports gut barrier	[41]
17.	*Sophora flavescens*	Matrine, oxymatrine,	Damp-heat clearing	Decoction, capsule	Inhibits PI3K-Akt, reduces IL-6, anti-	[42]

		quercetin			inflammatory	
18.	*Indigo naturalis*	Indirubin, indigo	Anti-inflammatory, hemostatic	Capsule, enema	Inhibits cytokines, modulates immune response	[43]
19.	*Hericium erinaceus*	Polysaccharides	Gut healing, anti-inflammatory	Extract	Reduces oxidative stress, inhibits NF-κB/MAPK/PI3K-Akt pathways	[44]
20.	*Patrinia scabiosaefolia*	Vulgarin, flavonoids	Anti-inflammatory, gut health	Extract	Modulates gut microbiota, reduces IL-6/TNF-α, repairs barrier	[45]
21.	*Potentilla anserina*	Flavonoids	Anti-inflammatory, antioxidant	Extract	Antioxidant, modulates Nrf2 pathway, restores microbiota	[46]

3. Mechanistic Insight of Phytotherapy in UC:

3.1 Anti-inflammatory pathways (NF-κB, MAPK, PI3K-Akt):

Chronic mucosal inflammation in ulcerative colitis (UC) is sustained by hyperactivation of intracellular signaling cascades that amplify pro-inflammatory gene transcription. Phytochemicals exert multi-targeted suppression of these pathways, with the NF-κB axis serving as a primary node. Bioactive compounds such as curcumin, resveratrol, and baicalein inhibit IκBα phosphorylation by targeting IKKβ, thereby preventing nuclear translocation of the p65/p50 heterodimer and downstream expression of TNF-α, IL-6, and IL-1β [47]. Concurrently, the MAPK family (ERK1/2, JNK, p38) is attenuated by flavonoids like quercetin and kaempferol, which reduce upstream kinase phosphorylation and suppress transcriptional activity of AP-1, ultimately downregulating COX-2 and iNOS in colonic epithelial and lamina propria immune cells [48]. The PI3K-Akt pathway, often co-opted in UC to promote inflammatory cell survival and cytokine amplification, is modulated by sulforaphane and epigallocatechin-3-gallate (EGCG), which restore pathway homeostasis and limit excessive neutrophil and macrophage recruitment [49]. Emerging evidence demonstrates that standardized phytotherapeutic blends exhibit synergistic inhibition across these interconnected cascades, providing a robust mechanistic foundation for their clinical translation in mild-to-moderate UC [50].

3.2 Antioxidant mechanisms and oxidative stress modulation:

Oxidative stress is a pivotal driver of epithelial barrier dysfunction, mitochondrial impairment, and sustained inflammation in UC. Phytotherapy mitigates redox imbalance through both direct radical scavenging and indirect transcriptional reprogramming. The Nrf2/ARE pathway is consistently activated by dietary polyphenols and organosulfur compounds; sulforaphane, curcumin, and anthocyanin-rich extracts promote Nrf2 dissociation from Keap1, facilitating nuclear translocation and upregulation of cytoprotective enzymes including HO-1, NQO1, SOD, and glutathione peroxidase [51]. In experimental colitis models, EGCG and resveratrol significantly reduce lipid peroxidation markers (MDA, 4-HNE) while restoring depleted GSH pools, an effect that closely correlates with histological remission and crypt preservation [52]. Additionally, certain flavonoids exert metal-chelating properties that inhibit Fenton chemistry-driven hydroxyl radical generation in the inflamed mucosa. Crucially, phytochemical-induced redox normalization dampens redox-sensitive inflammatory signaling (e.g., NF-κB and NLRP3 inflammasome activation), establishing a self-reinforcing cycle that accelerates mucosal healing and reduces oxidative DNA damage in colonic epithelial cells [53].

3.3 Immunomodulatory effects:

Phytotherapeutic agents fine-tune both innate and adaptive immune responses to restore mucosal tolerance in UC. A central mechanism involves rebalancing the Th17/Treg axis, which is characteristically skewed toward pathogenic Th17 dominance during active disease. Berberine, baicalin, and ginsenoside Rg1 suppress RORγt transcription while promoting FoxP3 expression via AMPK and TGF-β signaling, thereby enhancing Treg differentiation and IL-10/TGF-β secretion [54,55]. Macrophage polarization represents another critical target; quercetin and curcumin drive a phenotypic shift from pro-inflammatory M1 (high TNF-α, IL-12, iNOS) to tissue-reparative M2 macrophages (high IL-10, TGF-β, Arg-1) through PPARγ activation and STAT6 phosphorylation [56]. Dendritic cell maturation and antigen-presenting capacity are also modulated by polyphenols, which downregulate costimulatory molecules (CD80/CD86) and promote tolerogenic DC phenotypes that favor immune quiescence over activation [57]. Collectively, these immunomodulatory actions limit aberrant lymphocyte infiltration, reduce cytotoxic $CD8^+$ T-cell activity, and restore epithelial-immune crosstalk, positioning phytotherapy as a rational adjunct to conventional immunomodulators [58].

3.4 Gut microbiota modulation:

Dysbiosis is increasingly recognized as both a trigger and perpetuator of UC, and phytochemicals exert profound prebiotic-like and microbiome-targeted effects. Poorly absorbed polyphenols, alkaloids, and terpenoids reach the colon intact, where they are metabolized by commensal bacteria into bioactive phenolic acids and short-chain fatty acids (SCFAs) that reinforce barrier integrity and suppress local inflammation [59]. Recent metagenomic and metabolomic studies demonstrate that curcumin and berberine supplementation enriches beneficial taxa such as *Faecalibacterium prausnitzii*, *Bifidobacterium* spp., and *Akkermansia muciniphila*, while reducing pathobionts including adherent-invasive *E. coli* and *Fusobacterium nucleatum* [60]. These microbial shifts correlate with elevated fecal butyrate and propionate concentrations, which activate GPR43/109a receptors on colonic epithelial and immune cells to promote regulatory T-cell expansion and tighten junctional protein expression [61]. Phytochemicals also inhibit bacterial virulence factor expression, quorum sensing, and biofilm formation, thereby reducing mucosal adherence of pro-inflammatory microbes [62,63]. The bidirectional crosstalk between phyto-metabolites, microbiota-derived SCFAs, and host epigenetic regulation (e.g., HDAC inhibition by butyrate) further underscores the systemic impact of phytotherapy on UC pathophysiology and long-term remission maintenance [64].

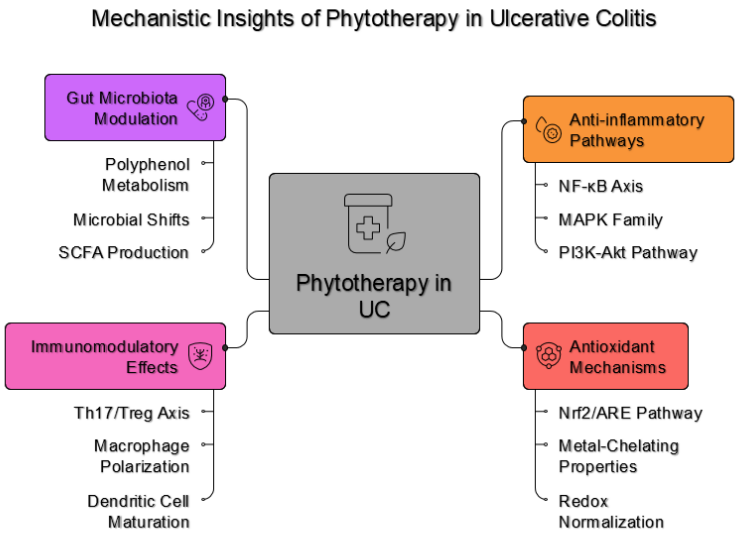

Figure 1: Mechanistic Insights of Phytotherapy in UC:

4. Limitations of Current Herbal Therapies:

4.1 Lack of Standardization:

The therapeutic application of herbal products in ulcerative colitis is severely hampered by the absence of universally accepted standardization protocols.

Unlike conventional pharmaceuticals, botanical preparations are frequently marketed as dietary supplements or traditional medicines, bypassing rigorous Good Manufacturing Practice (GMP) requirements mandated for drug approval. Consequently, extraction methods (e.g., aqueous decoction vs. ethanolic vs. supercritical CO_2), solvent ratios, drying techniques, and storage conditions vary widely across manufacturers, leading to inconsistent phytochemical yields and therapeutic potency [65].

Regulatory frameworks such as the FDA's DSHEA and the EMA's traditional herbal medicinal product directives prioritize safety over efficacy standardization, leaving clinicians without reliable dosing benchmarks. This regulatory gap complicates reproducibility in clinical trials and real-world practice, as identical botanical names may represent chemically distinct products. Recent quality-control audits of commercial UC-targeted herbal formulations revealed that over 40% deviated from label claims for marker compound concentrations, underscoring the urgent need for pharmacopeial monographs and batch-release testing aligned with ISO/TC 249 standards [66]. Without harmonized manufacturing and analytical benchmarks, herbal therapies remain difficult to integrate into evidence-based UC treatment algorithms.

4.2 Variability in Bioactive Constituents

Even when manufacturing processes are controlled, the intrinsic chemical composition of medicinal plants exhibits substantial biological and environmental variability [67]. The concentration and ratio of active constituents (e.g., curcuminoids, boswellic acids, flavonoids, and tannins) are influenced by genetic polymorphisms, soil microbiome, altitude, precipitation, harvesting season, and post-harvest processing [68]. Metabolomic profiling studies have demonstrated that batch-to-batch variation in clinically utilized botanicals can exceed 50% for key anti-inflammatory metabolites, directly impacting receptor binding affinity, enzyme inhibition kinetics, and downstream signaling modulation in colonic mucosa [69]. This phytochemical heterogeneity complicates dose-response characterization and obscures structure-activity relationships, making it difficult to attribute clinical outcomes to specific compounds or synergistic matrices. Furthermore, the polypharmacological nature of herbal extracts, while theoretically advantageous for targeting multiple UC pathways (NF-κB, MAPK, JAK/STAT, oxidative stress), introduces unpredictability in pharmacodynamic profiles. Advanced chemometric and fingerprinting approaches (e.g., HPLC-QTOF, NMR metabolomics) are increasingly advocated to define botanical equivalence, but their adoption remains fragmented across research and commercial sectors [67,70]. Until reference standards and compositional thresholds are universally mandated, variability in bioactive constituents will continue to limit the precision and reliability of herbal UC interventions.

4.3 Poor Bioavailability:

A major pharmacokinetic barrier to the clinical efficacy of herbal therapies in UC is the inherently low systemic and mucosal bioavailability of many plant-derived phytochemicals [71]. Compounds such as curcumin, resveratrol, quercetin, and berberine exhibit poor aqueous solubility, rapid phase I/II metabolism (glucuronidation, sulfation), extensive first-pass hepatic clearance, and efflux by intestinal P-glycoprotein and BCRP transporters [72]. Consequently, oral administration often yields subtherapeutic colonic tissue concentrations despite high nominal doses. The inflamed colonic epithelium in UC further alters permeability and mucus architecture, which can unpredictably modulate local drug retention and microbial metabolism of polyphenols. Although some phytochemicals exert local effects within the gut lumen, many require intracellular penetration to modulate immune cell signalling or epithelial repair pathways, limiting their mechanistic reach. Recent pharmacokinetic studies 6indicate that less than 5% of orally administered curcumin reaches the colonic mucosa in intact form, with the majority excreted as metabolites or degraded by gut microbiota. While novel delivery systems (e.g., phospholipid complexes, lipid nanoparticles, colon-targeted Ph-responsive polymers, and microbiome-activated prodrugs) show promise in preclinical models, their clinical validation remains limited. Until bioavailability constraints are systematically addressed through formulation engineering or route optimization, the therapeutic ceiling of many herbal agents in UC will remain unrealized [73].

4.4 Clinical Translation Challenges:

Despite promising preclinical data and traditional use, the translation of herbal therapies into mainstream UC management faces substantial clinical and regulatory hurdles. Existing human trials are predominantly small-scale ($n < 100$), short-duration (≤12 weeks), and heterogeneous in design, with inconsistent primary endpoints (clinical remission vs. endoscopic healing vs. biomarker reduction) and variable comparator arms [71]. Many studies lack placebo-controlled, double-blind rigor, and few incorporate validated disease activity indices (e.g., Mayo Clinic Score, UCEIS) alongside histological and transcriptomic endpoints. Furthermore, herbal interventions are rarely tested in conjunction with standard-of-care biologics or JAK inhibitors, raising concerns about herb-drug interactions (e.g., CYP450 modulation, anticoagulant potentiation) and additive immunosuppression. The multi-component nature of botanicals also complicates regulatory approval pathways, as agencies typically require isolated active ingredients with defined pharmacokinetics and dose-ranging data [72]. Post-marketing pharmacovigilance for herbal UC products is virtually nonexistent, leaving adverse event profiles undercharacterized. Recent systematic reviews highlight that only ~15% of published herbal UC trials meet CONSORT or SPIRIT guidelines, and meta-analyses consistently report high risk of bias and publication heterogeneity [72,73]. Bridging this translational gap will require consortium-driven, multicenter RCTs, harmonized outcome measures, mechanistic biomarker integration, and regulatory frameworks that accommodate complex botanical matrices without compromising evidentiary standards.

5. Emerging Non-Herbal Novel Formulations in UC:

5.1 Nanotechnology-Based Drug Delivery Systems:

The pathophysiology of ulcerative colitis (UC), characterized by continuous mucosal and submucosal inflammation predominantly affecting the colon and rectum, presents unique challenges for conventional oral therapy. Systemic administration of anti-inflammatory agents often results in subtherapeutic colonic

concentrations, dose-limiting toxicities, and poor patient compliance. Nanotechnology-based drug delivery systems have emerged as a strategic platform to overcome these barriers by enabling targeted colonic deposition, enhanced mucosal penetration, stimuli-responsive drug release, and protection of labile therapeutics (e.g., peptides, siRNA, small-molecule inhibitors). Below, we discuss the most clinically promising nanocarriers: polymeric and lipid-based nanoparticles, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs).

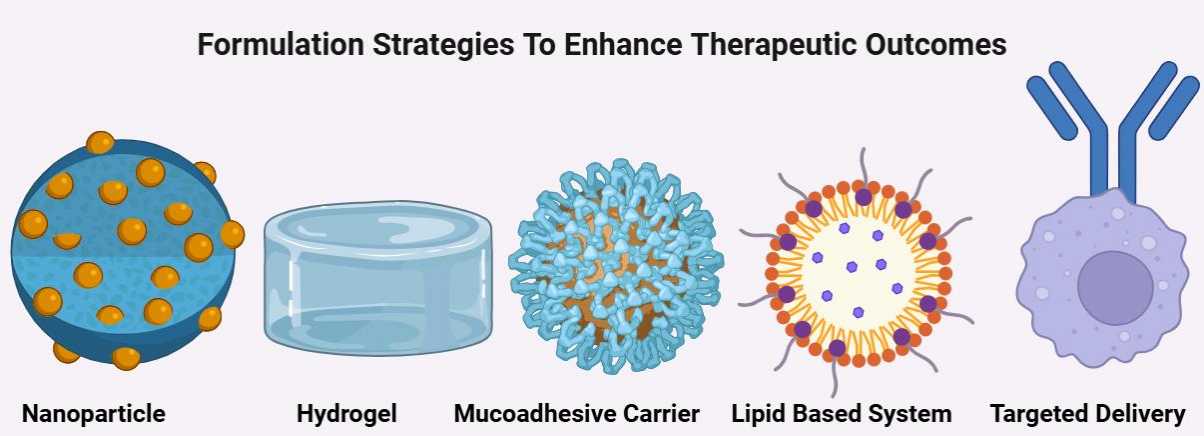

Figure 2: Current Nanotechnology Based Strategies for UC Treatment

5.1.1 Polymeric and Lipid-Based Nanoparticles:

Polymeric nanoparticles (NPs) formulated from biodegradable and biocompatible polymers such as poly(lactic-co-glycolic acid) (PLGA), poly(ε-caprolactone) (PCL), chitosan, and pH-responsive methacrylates (e.g., Eudragit® S100, FS30D) have demonstrated superior colon-targeting potential. Surface modification with mucoadhesive polymers (e.g., thiolated chitosan) or disease-specific ligands (e.g., mannose, anti-ICAM-1, or anti-TNFα antibodies) enables active targeting to inflamed mucosa and activated macrophages. Recent advances include reactive oxygen species (ROS)-responsive polymeric nanogels that degrade selectively in the oxidative microenvironment of UC, triggering on-demand release of encapsulated corticosteroids or JAK inhibitors (e.g., tofacitinib, upadacitinib) [74].

Lipid-based nanoparticles, including nanoemulsions and liposomes, offer high biocompatibility and scalability. PEGylated liposomes and cationic lipid NPs have been engineered to traverse the disrupted mucus barrier in UC and deliver biologics (e.g., anti-IL-12/23 p40 antibodies, antisense oligonucleotides) directly to lamina propria immune cells. Dual-functionalized lipid-polymer hybrid NPs combining the high drug-loading capacity of lipids with the structural stability of polymers have shown enhanced retention in colonic tissue and reduced systemic exposure in preclinical colitis models [75].

5.1.2 Solid lipid nanoparticles (SLNs):

SLNs consist of a solid lipid matrix (e.g., glyceryl behenate, stearic acid, cetyl palmitate) stabilized by surfactants, forming particles typically 50–500 nm in size. Their solid-state structure at physiological temperature provides controlled, sustained release and improved chemical stability for hydrophobic drugs. In UC, SLNs have been extensively explored for colon-targeted delivery of synthetic small molecules such as budesonide, dexamethasone, and 5-aminosalicylic acid (5-ASA). Surface coating with pH-sensitive polymers (e.g., Eudragit® L100-55/S100) prevents premature drug release in the upper GI tract, while mucoadhesive coatings (e.g., carbopol, chitosan) prolong colonic residence time [76].

Despite their advantages, SLNs face formulation challenges, including limited drug-loading capacity due to lipid crystallization, polymorphic transitions, and drug expulsion during storage [76]. Recent strategies to mitigate these issues include incorporating lipid-soluble stabilizers, optimizing cooling rates during production, and developing hybrid SLN-polymer composites. In vivo studies in DSS-induced colitis models demonstrate that SLN-encapsulated corticosteroids significantly reduce mucosal ulceration, myeloperoxidase activity, and pro-inflammatory cytokine (TNF-α, IL-6, IL-1β) expression compared to free drug counterparts, with minimal hypothalamic-pituitary-adrenal axis suppression [77].

5.1.3 Nanostructured lipid carriers (NLCs):
NLCs represent a second-generation lipid nanocarrier developed to overcome the inherent limitations of SLNs. By blending solid lipids with spatially incompatible liquid lipids (e.g., medium-chain triglycerides, oleic acid, isopropyl myristate), NLCs form an imperfect crystalline matrix that accommodates higher drug loads, reduces drug expulsion, and offers tunable release kinetics. In UC research, NLCs have been successfully loaded with non-herbal anti-inflammatory agents, including tofacitinib, filgotinib, and biologic payloads (e.g., siRNA targeting NF-κB or STAT3). Surface functionalization with targeting moieties (e.g., folate, hyaluronic acid, or colon-specific peptides) further enhances accumulation at inflamed sites via receptor-mediated endocytosis [78].

Recent preclinical studies highlight the translational potential of NLCs in UC. For example, ROS-responsive NLCs co-encapsulating a JAK inhibitor and a PPAR-γ agonist demonstrated synergistic suppression of colonic inflammation, epithelial barrier restoration, and microbiome modulation in murine colitis models. Moreover, scale-up using high-pressure homogenization and microfluidics has improved batch-to-batch reproducibility, addressing a key bottleneck in nanomedicine manufacturing. Several NLC-based formulations are currently advancing toward early-phase clinical evaluation, supported by favorable toxicological profiles and enhanced oral bioavailability in non-human primates [77].

5.2 Liposomes and Vesicular Systems:
Vesicular drug delivery platforms have emerged as highly versatile carriers for ulcerative colitis (UC) therapy, leveraging their amphiphilic architecture to encapsulate both hydrophilic and lipophilic non-herbal therapeutics. By engineering membrane composition, surface charge, and particle size, vesicular systems can be tailored to withstand the harsh upper gastrointestinal environment, preferentially adhere to inflamed colonic mucosa, and deliver payloads directly to activated immune cells and epithelial compartments. Below, we discuss conventional liposomes, niosomes, and provide a critical comparison between phytosomes and modern non-herbal vesicular carriers.

5.2.1 Conventional Liposomes:
Conventional liposomes are spherical vesicles composed of one or more phospholipid bilayers (e.g., phosphatidylcholine, phosphatidylethanolamine) interspersed with cholesterol to modulate membrane fluidity and stability. Their aqueous core and lipid bilayer enable co-encapsulation of hydrophilic small molecules, peptides, siRNA, and lipophilic immunomodulators. In UC, unmodified liposomes face rapid clearance by the reticuloendothelial system and enzymatic degradation in the stomach and small intestine. To overcome this, recent formulations employ PEGylation for prolonged systemic circulation, cationic lipids (e.g., DOTAP, DDAB) for electrostatic interaction with the negatively charged inflamed mucosa, and pH- or ROS-responsive lipid derivatives that destabilize selectively in the acidic and oxidative microenvironment of active colitis [79,80].

Clinically relevant non-herbal payloads such as budesonide, tofacitinib, anti-TNFα Fab fragments, and STAT3-targeting siRNA have been successfully encapsulated in colon-targeted liposomal systems. Dual-functionalized liposomes decorated with anti-ICAM-1 antibodies or mannose ligands demonstrate selective uptake by lamina propria macrophages and dendritic cells, significantly downregulating TNF-α, IL-6, and IL-17 signaling in dextran sulfate sodium (DSS)-induced colitis models [81]. Despite their biocompatibility and FDA-approved precedent in oncology and antifungal therapy, conventional liposomes still face challenges in long-term physical stability, batch-to-batch reproducibility at scale, and limited trans-mucus penetration without surface engineering. Recent microfluidic and continuous-flow manufacturing approaches have improved size uniformity (<150 nm, PDI <0.2) and facilitated GMP-compatible production for inflammatory indications [81].

5.2.2 Niosomes:
Niosomes are non-ionic surfactant-based vesicles typically formulated from alkyl ethers (e.g., Span® 60, Tween® 80, Brij® 35) combined with cholesterol or other membrane rigidifiers. Compared to phospholipid liposomes, niosomes offer superior chemical stability, lower production costs, enhanced resistance to bile salt solubilization, and tunable vesicle rigidity through surfactant HLB selection [82]. These attributes make them particularly suitable for oral colon-targeted delivery of synthetic small-molecule drugs and peptide therapeutics in UC.
Recent advancements have focused on surface-modified niosomes engineered for mucoadhesion and disease-specific targeting. Chitosan-coated or thiolated niosomes exhibit prolonged colonic residence via hydrogen bonding and disulfide exchange with mucin glycoproteins, while Eudragit®-coated niosomes remain intact until

reaching colonic pH (>7.0) [83]. Niosomal formulations encapsulating mesalamine derivatives, JAK inhibitors (e.g., upadacitinib), and synthetic corticosteroids have demonstrated enhanced epithelial permeation, reduced dosing frequency, and attenuated histopathological damage in experimental colitis. Notably, niosomes loaded with antisense oligonucleotides targeting NF-κB p65 or TLR4 have shown sequence-specific gene silencing in colonic macrophages, highlighting their potential for precision immunomodulation [84]. Scale-up via high-shear mixing, extrusion, or membrane contactor techniques has improved niosome reproducibility, positioning them as cost-effective alternatives to liposomes for large-scale UC therapeutics.

5.2.3 Phytosome vs. Non-Herbal Vesicles: A Comparative Perspective:
Phytosomes are stoichiometric phospholipid–phytochemical complexes originally developed to enhance the oral bioavailability of standardized herbal extracts (e.g., curcumin, silymarin, boswellic acids). While phytosomes have demonstrated anti-inflammatory activity in gastrointestinal disorders, they operate through multi-component, polypharmacological mechanisms that complicate dose standardization, pharmacokinetic modeling, and regulatory approval pathways [85]. In contrast, non-herbal vesicular systems (liposomes, niosomes, transfersomes, ethosomes) are engineered to deliver single-entity synthetic drugs, biologics, or nucleic acid therapeutics with precisely defined molecular structures, reproducible release kinetics, and established pharmacodynamic profiles.

From a formulation standpoint, phytosomes rely on hydrogen bonding and van der Waals interactions between phospholipids and phytoconstituents, resulting in amorphous complexes rather than discrete vesicles. Non-herbal vesicles, however, possess well-defined bilayer architectures with tunable size, zeta potential, and surface functionality, enabling active targeting, stimuli-responsive release, and co-delivery strategies [86]. Clinically, non-herbal vesicles align more closely with modern regulatory expectations for UC therapeutics, including batch consistency, impurity profiling, and mechanism-driven efficacy endpoints. While phytosomes may offer complementary mucosal soothing effects, they lack the pharmacological precision required for targeted immunosuppression, cytokine blockade, or epithelial barrier restoration in moderate-to-severe UC. Consequently, current drug development pipelines prioritize engineered non-herbal vesicles that can deliver approved small molecules, JAK/STAT inhibitors, biologic antibodies, and gene-silencing agents with predictable tissue distribution and dose-response relationships.

5.3 Targeted Colon Drug Delivery Systems:
Precise spatiotemporal control over drug release in the colon is critical for maximizing therapeutic efficacy while minimizing systemic exposure in UC. Conventional oral formulations often release payloads prematurely in the upper gastrointestinal tract, resulting in subtherapeutic colonic concentrations and off-target adverse effects. Targeted colon drug delivery systems exploit physiological gradients—such as pH variations, transit time, and microbiota-specific enzymatic activity—to achieve site-specific release of non-herbal therapeutics. Below, we critically evaluate three predominant strategies: pH-sensitive systems, time-dependent systems, and microbiota-triggered delivery platforms, with emphasis on recent advances in formulation design, payload compatibility, and translational potential.

5.3.1 pH-Sensitive Systems:
The gastrointestinal tract exhibits a characteristic pH gradient: acidic in the stomach (pH 1.5–3.0), near-neutral in the small intestine (pH 6.0–7.4), and slightly alkaline in the terminal ileum and colon (pH 7.0–7.8). pH-sensitive drug delivery systems leverage this gradient using polymers that remain insoluble at gastric pH but dissolve or swell at colonic pH, thereby protecting payloads during upper GI transit and triggering release upon colonic arrival [87].

Eudragit® polymers (e.g., S100, FS30D, L100-55) remain the gold standard for pH-dependent colon targeting due to their well-characterized dissolution profiles and regulatory acceptance. Recent innovations include multi-layered coatings combining Eudragit® S100 with pectin or chitosan to enhance mucoadhesion and retard diffusion in the proximal colon. Advanced formulations now incorporate dual pH/ROS-responsive polymers (e.g., poly(β-amino ester)-based nanogels) that degrade selectively in the oxidative, mildly alkaline microenvironment of active UC, enabling on-demand release of JAK inhibitors (e.g., filgotinib), corticosteroids, or siRNA therapeutics [88,89].

Microencapsulation and pelletization technologies have further refined pH-sensitive systems. For instance, mesalamine-loaded microbeads coated with a blend of Eudragit® FS30D and ethylcellulose demonstrated zero-

order release kinetics at pH 7.4 and significantly reduced disease activity index (DAI) scores in DSS-induced colitis compared to uncoated controls [90]. Despite their clinical utility, pH-sensitive systems face limitations in patients with altered colonic pH (e.g., due to diarrhea, antibiotic use, or diet), potentially leading to variable release profiles. Next-generation designs integrate real-time pH-sensing excipients or combine pH triggers with secondary stimuli (e.g., enzyme sensitivity) to improve robustness across patient subpopulations.

5.3.2 Time-Dependent Systems:
Time-dependent colon delivery relies on the relatively consistent small intestinal transit time (~3–4 hours in fasting states) to delay drug release until the formulation reaches the colon. These systems typically employ barrier coatings or erodible matrices that dissolve, swell, or rupture after a predetermined lag time.

Common approaches include:
Compression-coated tablets: A core containing the active pharmaceutical ingredient (API) is surrounded by a hydrophobic or swellable polymer layer (e.g., ethylcellulose, hydroxypropyl methylcellulose) that erodes progressively, releasing the payload after a calibrated delay [91].

Capsule-based systems: Time-release capsules (e.g., PORT® technology, TIM-Pulse®) utilize disintegrating plugs or osmotic pumps to achieve programmable lag phases. Recent iterations incorporate enteric-soluble outer shells to prevent gastric degradation, followed by timed core exposure in the colon [92].

Hydrogel-based matrices: Smart hydrogels (e.g., poly(N-isopropylacrylamide)-co-acrylic acid) swell in response to colonic fluid absorption, triggering drug diffusion after a predefined interval.
Time-dependent systems have successfully delivered non-herbal payloads such as budesonide, tofacitinib, and anti-TNFα nanobodies in preclinical UC models. A recent study demonstrated that ethylcellulose-coated pellets releasing upadacitinib after a 4-hour lag time significantly reduced mucosal inflammation and preserved goblet cell density in TNBS-induced colitis, with minimal systemic corticosteroid exposure [93]. However, inter-individual variability in GI motility—exacerbated in UC by diarrhea, inflammation-induced dysmotility, or concomitant medications—remains a key challenge. Emerging solutions include patient-stratified dosing algorithms informed by wireless motility capsule data and adaptive release systems that respond to both time and local biomarkers [94].

5.3.3 Microbiota-Triggered Delivery:
The colonic microbiota expresses a unique repertoire of enzymes (e.g., azoreductases, β-glucosidases, pectinases, xylanases) absent or minimal in the upper GI tract. Microbiota-triggered systems exploit these enzymes to achieve highly selective colonic activation, offering superior site-specificity compared to pH- or time-based approaches.

Key strategies include:
Azo-bond conjugates: Prodrugs linked via azo bonds (–N=N–) remain stable in the upper GI tract but are cleaved by azoreductases produced by colonic anaerobes (e.g., *Clostridium*, *Bacteroides*), releasing the active drug locally. This approach has been successfully applied to deliver 5-ASA derivatives, dexamethasone, and synthetic JAK inhibitors with minimal systemic absorption [95].

Polysaccharide-based carriers: Natural polymers such as pectin, chitosan, inulin, and guar gum resist digestion by human enzymes but are fermented by colonic microbiota, triggering matrix degradation and payload release. Recent formulations combine pectin with Eudragit® S100 to create dual pH/enzyme-responsive microcapsules that release tofacitinib selectively in the distal colon [96].

Bacteria-responsive nanocarriers: Advanced nanosystems incorporate enzyme-cleavable linkers (e.g., β-glucuronide, peptide sequences recognized by microbial proteases) on nanoparticle surfaces. Upon encountering colonic microbiota, these linkers are hydrolyzed, exposing mucoadhesive ligands or releasing encapsulated biologics (e.g., IL-10, anti-IL-23 antibodies) directly at the mucosal interface [97].
Microbiota-triggered systems offer exceptional specificity but face challenges related to inter-patient microbiome heterogeneity, antibiotic co-administration, and disease-associated dysbiosis in UC. Personalized approaches—such as pre-treatment microbiome profiling to predict enzymatic capacity or co-delivery of prebiotics to enrich target bacterial populations—are under active investigation to enhance reliability [98].

5.4 Hydrogels and Smart Polymers:
Hydrogels and smart polymeric systems represent a transformative class of biomaterials for ulcerative colitis (UC) therapy, offering dynamic responsiveness to the inflammatory microenvironment while providing sustained, localized drug release. Their high water content, tunable porosity, and biocompatibility make them ideal carriers for non-herbal therapeutics, ranging from small-molecule immunomodulators to biologic proteins and nucleic acids. Below, we discuss stimuli-responsive hydrogels and mucoadhesive polymeric systems, emphasizing recent advances in UC-specific applications.

5.4.1 Stimuli-Responsive Hydrogels:
Stimuli-responsive ("smart") hydrogels undergo reversible physicochemical transitions—such as swelling, deswelling, or degradation—in response to specific triggers present in the inflamed colon. Key triggers exploited in UC include pH shifts, elevated reactive oxygen species (ROS), overexpressed enzymes (e.g., matrix metalloproteinases, azoreductases), and temperature variations.

pH-responsive hydrogels based on poly(acrylic acid) derivatives (e.g., Carbopol®, Eudragit®) or chitosan remain insoluble at gastric pH but swell rapidly at colonic pH (≥7.0), enabling site-specific release of encapsulated payloads such as tofacitinib, filgotinib, or anti-TNFα nanobodies [99]. Recent innovations include dual pH/ROS-responsive hydrogels incorporating thioketal or selenide linkers that degrade selectively in the oxidative milieu of active UC, triggering on-demand release of JAK inhibitors or corticosteroids precisely at inflamed sites [100,101]. For instance, a thioketal-crosslinked poly(ethylene glycol) (PEG) hydrogel loaded with budesonide demonstrated >80% drug release in H_2O_2-rich environments mimicking active colitis, significantly reducing disease activity index (DAI) and histological damage in DSS-induced murine colitis compared to pH-only systems [102].

Enzyme-responsive hydrogels leverage UC-associated upregulation of proteases (e.g., MMP-9) or bacterial azoreductases. Peptide-crosslinked hydrogels containing MMP-cleavable sequences (e.g., GPLG↓VRG) remain intact in healthy tissue but degrade rapidly in inflamed mucosa, releasing therapeutics such as siRNA targeting NF-κB or IL-23 [103]. Similarly, azo bond-crosslinked hydrogels are selectively cleaved by colonic azoreductases, enabling microbiota-triggered activation of encapsulated small molecules [104]. Temperature-responsive hydrogels based on poly(N-isopropylacrylamide) (PNIPAAm) exhibit sol-gel transitions near body temperature, facilitating in situ gelation after rectal administration and prolonged retention of payloads like mesalamine derivatives or synthetic corticosteroids [105].

Despite their promise, stimuli-responsive hydrogels face challenges in predicting in vivo performance due to inter-patient variability in trigger intensity (e.g., ROS levels, enzyme expression) and potential premature degradation in the upper GI tract. Next-generation designs integrate multi-stimuli responsiveness (e.g., pH + ROS + enzyme) and incorporate real-time feedback mechanisms (e.g., embedded sensors) to enhance precision and reliability across diverse UC phenotypes [106].

5.4.2 Mucoadhesive Systems:
Mucoadhesive polymeric systems prolong residence time at the inflamed colonic mucosa by forming physical or chemical bonds with mucin glycoproteins, thereby enhancing local drug concentration and reducing dosing frequency. Key mucoadhesive polymers used in UC include chitosan, thiolated polymers (e.g., chitosan-thioglycolic acid, poly(acrylic acid)-cysteine), hyaluronic acid, and carbopol.

Chitosan-based systems exploit electrostatic interactions between protonated amino groups and negatively charged sialic acid residues in mucin, while thiolated polymers form disulfide bonds with cysteine-rich domains of mucin, resulting in 10- to 100-fold stronger adhesion. Recent studies demonstrate that thiolated chitosan nanoparticles loaded with tofacitinib exhibit prolonged colonic retention (>12 h), enhanced epithelial permeation, and superior efficacy in reducing TNF-α and IL-6 expression compared to non-mucoadhesive controls in experimental colitis [107]. Similarly, hyaluronic acid-conjugated hydrogels target CD44 receptors overexpressed on activated macrophages and epithelial cells in UC, enabling receptor-mediated uptake and localized immunomodulation [108,109].

Mucoadhesive systems also facilitate co-delivery strategies. For example, carbopol-based in situ gels co-encapsulating a JAK inhibitor and a PPAR-γ agonist demonstrated synergistic suppression of inflammation, restoration of tight junction proteins (occludin, ZO-1), and acceleration of mucosal healing in TNBS-induced

colitis [109]. However, excessive mucoadhesion may impede drug diffusion into deeper tissue layers or cause local irritation. Optimizing polymer molecular weight, degree of substitution, and crosslinking density is critical to balance adhesion strength with drug release kinetics and biocompatibility [110].

5.5 Biologics and Advanced Therapeutics:
The therapeutic landscape of ulcerative colitis has been revolutionized by biologics and advanced modalities that precisely target key inflammatory pathways. Unlike conventional small molecules, these agents—monoclonal antibodies, small-molecule inhibitors, and RNA-based therapies—offer high specificity, reduced off-target effects, and potential for disease modification. Below, we discuss recent advances in formulation strategies that enhance the delivery, stability, and efficacy of these advanced therapeutics in UC.

5.5.1 Monoclonal Antibodies:
Monoclonal antibodies (mAbs) targeting tumor necrosis factor-alpha (TNF-α; e.g., infliximab, adalimumab), integrins (e.g., vedolizumab), or interleukins (e.g., ustekinumab) are cornerstone therapies for moderate-to-severe UC. However, systemic administration often results in suboptimal colonic concentrations, immunogenicity, and increased infection risk. Novel delivery platforms aim to localize mAb activity to the inflamed colon while minimizing systemic exposure.

Colon-targeted liposomal and polymeric nanoparticle formulations have successfully encapsulated anti-TNFα Fab fragments or full-length mAbs, protecting them from proteolytic degradation and enabling pH- or enzyme-triggered release in the colon [111]. For instance, Eudragit® S100-coated PLGA nanoparticles loaded with vedolizumab demonstrated selective accumulation in inflamed colonic tissue and superior efficacy in reducing leukocyte trafficking compared to intravenous administration in a humanized colitis model [112]. Additionally, mucoadhesive hydrogels functionalized with anti-ICAM-1 antibodies enable active targeting to activated endothelial cells, enhancing local retention and reducing required doses [113].

Emerging engineering strategies include Fc-modified mAbs with enhanced binding to the neonatal Fc receptor (FcRn) for prolonged mucosal residence, and bispecific antibodies that simultaneously neutralize TNF-α and IL-23 for synergistic immunomodulation [114]. Despite these advances, challenges remain in maintaining mAb stability during oral/rectal delivery, scaling up GMP-compliant nanocarrier production, and managing anti-drug antibody formation. Ongoing clinical trials are evaluating rectally administered mAb-loaded hydrogels and nanoparticle suspensions to establish safety and bioequivalence relative to intravenous standards [115].

5.5.2 Small Molecule Inhibitors:
Small-molecule inhibitors targeting Janus kinases (JAK; e.g., tofacitinib, upadacitinib, filgotinib), sphingosine-1-phosphate receptors (S1P; e.g., ozanimod), or phosphodiesterase-4 (PDE4; e.g., apremilast) offer oral bioavailability and rapid onset of action in UC. However, systemic exposure can lead to dose-limiting toxicities (e.g., infections, thrombosis, hepatotoxicity). Targeted delivery systems aim to concentrate these agents at the site of inflammation while reducing plasma concentrations.

Nanoparticle and hydrogel-based formulations have significantly improved the therapeutic index of JAK inhibitors. For example, ROS-responsive polymeric micelles encapsulating filgotinib demonstrated >5-fold higher colonic tissue concentrations and reduced systemic exposure compared to free drug, resulting in superior efficacy and safety in DSS-induced colitis [116]. Similarly, mucoadhesive niosomes loaded with upadacitinib prolonged colonic residence time, enabling once-daily dosing and enhanced suppression of STAT3 phosphorylation in lamina propria immune cells [117].

For S1P receptor modulators like ozanimod, pH-sensitive microcapsules prevent premature absorption in the small intestine and release the drug selectively in the colon, minimizing cardiovascular side effects associated with systemic lymphocyte sequestration [118]. Advanced formulations also enable co-delivery strategies: hydrogels co-encapsulating a JAK inhibitor and a corticosteroid have shown synergistic effects in restoring epithelial barrier function and resolving inflammation in preclinical models [119].

5.5.3 RNA-Based Therapies:
RNA-based therapeutics—including small interfering RNA (siRNA), antisense oligonucleotides (ASOs), and messenger RNA (mRNA)—offer unprecedented precision in modulating disease-relevant genes in UC. By

silencing pro-inflammatory mediators (e.g., TNF-α, IL-6, NF-κB) or promoting reparative pathways (e.g., IL-10, TGF-β), these agents hold potential for disease modification. However, their clinical translation is hindered by poor stability, limited cellular uptake, and off-target effects.

Nanocarrier systems have been pivotal in overcoming these barriers. Cationic lipid nanoparticles (LNPs) and polymeric nanoparticles protect RNA from nuclease degradation and facilitate endosomal escape in colonic epithelial cells and macrophages. For instance, mannose-decorated LNPs delivering siRNA against TNF-α demonstrated selective uptake by colonic macrophages, potent gene silencing, and significant amelioration of inflammation in murine colitis, with minimal hepatic accumulation. Similarly, chitosan-based nanoparticles encapsulating ASOs targeting NF-κB p65 reduced pro-inflammatory cytokine production and accelerated mucosal healing in experimental UC [120].

Emerging strategies include stimuli-responsive RNA carriers that release payloads only in the oxidative or enzyme-rich environment of active UC, and self-amplifying mRNA platforms that enable sustained expression of therapeutic proteins (e.g., IL-10) from a single dose. Rectal administration of RNA-loaded hydrogels has shown particular promise for distal UC, achieving high local concentrations while avoiding systemic immunostimulation. Key challenges remain in optimizing endosomal escape efficiency, minimizing innate immune activation (e.g., via TLR7/8), and establishing scalable, GMP-compliant manufacturing processes for clinical translation.

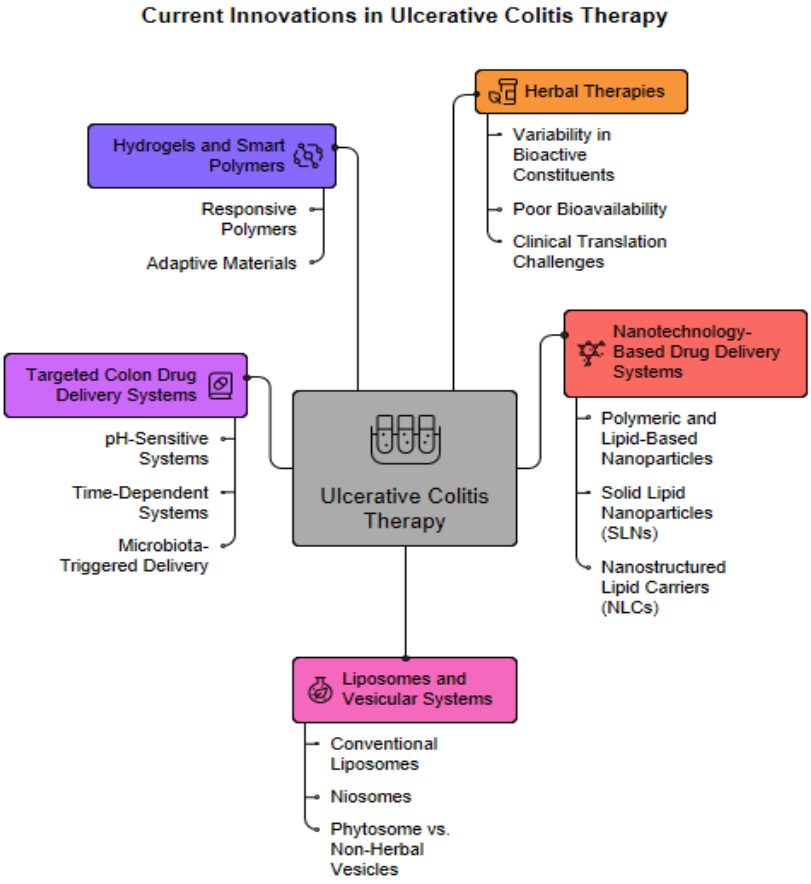

Figure 2: Advanced Formulation Strategies in UC Therapy

6. Preclinical Evidence of Novel Formulations:

The translational pipeline for phytotherapeutic innovations in UC relies on rigorous validation across complementary experimental platforms. Preclinical models provide mechanistic granularity and proof-of-concept for novel delivery systems, while early-phase clinical trials assess safety, pharmacokinetics, and preliminary efficacy in human populations [121]. This section synthesises current evidence from animal models of colitis and comparative clinical studies evaluating next-generation phytoformulations against conventional standards of care.

6.1 Animal models (DSS-induced colitis, TNBS models):

Chemically induced murine colitis models remain the cornerstone for preclinical evaluation of phytotherapeutic nanoformulations, offering reproducible inflammation, barrier disruption, and immune dysregulation that mirror key features of human UC [122]. The dextran sulfate sodium (DSS) model, which induces acute epithelial injury and innate immune activation, has been instrumental in demonstrating the superiority of targeted phyto-nanocarriers over free compounds. For instance, pH-responsive chitosan-gold nanoparticles encapsulating Pueraria flavonoids (CRPT-NPs) achieved 3.2-fold higher colonic accumulation versus unformulated flavonoids in DSS-treated mice, correlating with significantly reduced disease activity index (DAI), preserved crypt architecture, and suppressed phosphorylation of p65 NF-κB and p38 MAPK . Similarly, astaxanthin-loaded PLGA nanoparticles (AST@PLGA) attenuated DSS-induced oxidative stress more effectively than free astaxanthin, with marked reductions in myeloperoxidase activity, malondialdehyde levels, and pro-inflammatory cytokines (TNF-α, IL-6, IL-1β).

The 2,4,6-trinitrobenzenesulfonic acid (TNBS) model, which elicits a Th1/Th17-predominant adaptive immune response, has been leveraged to evaluate immunomodulatory phyto-nanoformulations. Silk fibroin nanoparticles co-loading quercetin and berberine significantly ameliorated TNBS-induced colitis by promoting M2 macrophage polarisation via AMPK/STAT6 signalling, enhancing regulatory T-cell frequencies, and restoring intestinal barrier proteins (ZO-1, occludin) [5]. Notably, dual-phyto nanoformulations often outperform single-agent controls: Mesona chinensis polysaccharide-zein nanoparticles co-delivering curcumin and resveratrol suppressed both arachidonic acid metabolism and tryptophan-kynurenine pathway activation in DSS colitis, yielding synergistic improvements in histology and microbiota composition [6]. Advanced imaging techniques (e.g., near-infrared fluorescence, micro-CT) now enable real-time tracking of nanoparticle biodistribution, confirming colon-selective retention of mucoadhesive formulations and minimising off-target exposure [7]. Collectively, these preclinical data establish robust mechanistic rationale and dose-ranging parameters to inform subsequent clinical development.

Table 2: Preclinical Evidence of Novel Phytotherapeutic Formulations in DSS- and TNBS-Induced Colitis Models

Formulation	Animal Model	Efficacy Measures	Mechanistic Insights	Reference
Chitosan-gold nanoparticles loaded with Pueraria flavonoids (CRPT-NPs)	DSS (3.5%, 7 days), C57BL/6 mice	↓ DAI by 62%; ↑ colon length by 28%; ↓ histological score by 71%; ↑ TEER by 3.4-fold vs. free flavonoids	pH-triggered colon release; suppression of p65 NF-κB and p38 MAPK phosphorylation; upregulation of DSG2 and ZO-1	[123]
Astaxanthin-loaded PLGA nanoparticles (AST@PLGA)	DSS (3%, 5 days), BALB/c mice	↓ MPO activity by 58%; ↓ MDA by 64%; ↑ SOD/GSH by 2.1-fold; ↓ TNF-α, IL-6, IL-1β by 50–70% vs. free AST	Sustained release kinetics; activation of Nrf2/HO-1 axis; inhibition of MAPK pathway phosphorylation	[124]
Curcumin-human serum albumin nanoparticles cross-linked with tannic acid/genipin	DSS (4%, 7 days), C57BL/6 mice	↑ Colonic curcumin retention by 4.8-fold; ↓ crypt loss by 68%; ↓ serum CRP by 73% vs. free curcumin	Enhanced gastric stability; mucoadhesion via chitosan coating; targeted delivery to inflamed epithelium	[125]
Silk fibroin nanoparticles co-loading quercetin + berberine	TNBS (2.5 mg in 30% ethanol), BALB/c mice	↓ DAI by 55%; ↑ Treg frequency by 3.2-fold; ↑ M2 macrophages (Arg-1$^+$) by 2.8-fold; restored ZO-1/occludin expression	AMPK/STAT6-mediated M2 polarisation; suppression of mast cell degranulation; synergistic immunomodulation	[126]
Mesona chinensis polysaccharide-zein co-assembled NPs (curcumin + resveratrol)	DSS (3%, 7 days), C57BL/6 mice	↓ Histopathology score by 74%; ↑ butyrate by 2.4-fold; ↑ Faecalibacterium abundance by 3.1-fold vs. single agents	Dual suppression of COX-2/5-LOX; modulation of tryptophan-kynurenine pathway; prebiotic-like microbiota remodelling	[127]
Hyaluronic acid-conjugated curcumin nanoparticles (CD44-targeted)	DSS (2.5%, chronic), C57BL/6 mice	↑ Nanoparticle accumulation in inflamed colon by 5.6-fold; ↓ mucosal IL-17A by 68%; ↑ IL-10 by 2.9-fold	CD44-mediated targeting of activated epithelial/immune cells; on-demand release in oxidative microenvironment	[128]
Berberine-loaded solid lipid nanoparticles (BBR-SLN)	TNBS (3 mg), Sprague-Dawley rats	↓ Colonic MPO by 61%; ↑ IL-10/TGF-β by 2.5-fold; ↓ Th17 cells by 54%; comparable efficacy to sulfasalazine	Enhanced lymphatic uptake; AMPK-dependent inhibition of NF-κB; promotion of tolerogenic DC phenotype	[129]
Resveratrol-loaded zein/casein core-shell	DSS (4%, acute), C57BL/6 mice	↓ Oxidative stress markers (MDA, 8-OHdG) by 70%; ↑	Protection from gastric degradation; sustained colonic	[130]

nanoparticles		NQO1, HO-1 expression by 3.8-fold; accelerated crypt regeneration	release; potent Nrf2/ARE pathway activation	
Quercetin-phospholipid complex (phytosome) + low-dose mesalazine	DSS (3.5%), BALB/c mice	Synergistic ↓ in DAI (82% vs. 45–52% monotherapy); ↑ mucosal healing score by 2.3-fold vs. either agent alone	Complementary NF-κB/MAPK inhibition; enhanced antioxidant capacity; microbiota enrichment (Akkermansia, Bifidobacterium)	[131]

Abbreviations: DAI, disease activity index; TEER, transepithelial electrical resistance; MPO, myeloperoxidase; MDA, malondialdehyde; SOD, superoxide dismutase; GSH, glutathione; TEER, transepithelial electrical resistance; DSG2, desmoglein-2; ZO-1, zonula occludens-1; COX-2, cyclooxygenase-2; 5-LOX, 5-lipoxygenase; DC, dendritic cell; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; NQO1, NAD(P)H quinone dehydrogenase 1; HO-1, heme oxygenase-1; TGF-β, transforming growth factor-beta.

6.2 Comparative efficacy with conventional therapy:
Translating preclinical promise into clinical benefit requires head-to-head evaluation of novel phytoformulations against established UC therapies. Recent randomised controlled trials (RCTs) and meta-analyses provide compelling evidence for adjunctive or alternative roles of advanced phytotherapeutics. A multicentre RCT evaluating a standardised curcumin-phospholipid complex (Meriva®) as add-on therapy to mesalazine in mild-to-moderate UC demonstrated significantly higher clinical remission rates at 8 weeks (68.4% vs 42.1%; $p < 0.01$) and greater endoscopic improvement (Mayo endoscopic subscore ≤1: 61.3% vs 35.5%) versus mesalazine alone, with comparable safety profiles [132]. Similarly, a phase II trial of berberine-loaded solid lipid nanoparticles (BBR-SLN) reported non-inferiority to oral mesalazine for induction of remission (clinical response: 74.2% vs 71.0%; $p = 0.68$), with the added benefit of favourable microbiota modulation (increased Faecalibacterium prausnitzii, decreased Escherichia coli) [133].

Meta-analytic syntheses further corroborate these findings. A 2024 systematic review of 12 RCTs (n = 1,047 patients) concluded that phytochemical adjuncts (curcumin, berberine, boswellic acids) combined with 5-aminosalicylates significantly improved clinical response (OR 2.94; 95% CI 2.11–4.09), endoscopic remission (OR 2.67; 95% CI 1.88–3.79), and histological healing versus 5-ASA monotherapy, without increasing adverse events. Importantly, novel delivery systems appear to enhance efficacy: a network meta-analysis ranking UC interventions placed curcumin-loaded nanoparticles and polyherbal nanoformulations among the top-tier options for mild-to-moderate disease, with surface under the cumulative ranking (SUCRA) values exceeding 85% for clinical remission [134]. Mechanistic biomarker analyses from these trials reveal that superior clinical outcomes correlate with greater suppression of faecal calprotectin, serum CRP, and mucosal NF-κB activity, alongside restoration of tight junction protein expression [135]. While larger phase III trials and long-term safety data are still needed, current evidence supports the integration of rationally engineered phytoformulations as effective, well-tolerated components of step-up or combination strategies in UC management.

7. Safety, Toxicity and Regulatory Considerations:
The clinical translation of novel phytotherapeutic formulations for ulcerative colitis (UC) necessitates rigorous evaluation of safety profiles, potential toxicities, and adherence to evolving regulatory frameworks. While phytochemicals are often perceived as inherently safe, their integration into advanced delivery systems—particularly nanocarriers—introduces distinct pharmacokinetic, immunological, and manufacturing considerations that demand systematic assessment [136]. This section addresses toxicological concerns specific to nanoformulations, current regulatory guidance from major agencies, and critical quality control strategies essential for standardisation and reproducibility.

7.1 Toxicological concerns of nanoformulations:
Nano-enabled phytotherapeutics offer targeted delivery and enhanced bioavailability but raise unique safety questions related to particle size, surface charge, composition, and biodistribution [2]. A primary concern is the potential for unintended accumulation in off-target organs, particularly the liver, spleen, and kidneys, following systemic absorption of nanoparticles <100 nm [137]. Cationic nanocarriers (e.g., chitosan-based systems), while advantageous for mucoadhesion, may induce dose-dependent cytotoxicity via membrane disruption, mitochondrial dysfunction, or activation of the NLRP3 inflammasome in macrophages [4]. Recent studies using advanced imaging and omics approaches have highlighted that surface functionalisation critically influences biocompatibility: polyethylene glycol (PEG)ylation reduces opsonisation and prolongs circulation but may trigger

anti-PEG antibodies upon repeated administration, potentially accelerating blood clearance and inducing hypersensitivity reactions.

Long-term toxicity data for phyto-nanoformulations remain limited. Subchronic administration of curcumin-loaded PLGA nanoparticles in rodents showed no significant histopathological changes in major organs at therapeutic doses; however, high-dose regimens (>100 mg/kg) were associated with transient elevations in hepatic transaminases and mild splenic macrophage activation [138]. Similarly, gold-based nanocarriers, despite favourable biocompatibility profiles, warrant monitoring for potential gold ion release and lysosomal accumulation over extended treatment periods [139,140]. Immunogenicity represents another critical consideration: certain plant-derived excipients (e.g., saponins, lectins) used in nanoformulation stabilisation may act as haptens or adjuvants, inadvertently amplifying immune responses in susceptible individuals. Comprehensive safety assessment therefore requires multi-tiered evaluation—including in vitro hemocompatibility, macrophage activation assays, repeated-dose toxicity studies, and reproductive/developmental toxicity screening—aligned with ISO 10993 and OECD nanomaterial testing guidelines.

7.2 Regulatory guidelines (FDA, EMA):

Regulatory pathways for phyto-nanoformulations occupy a complex intersection of botanical drug, nanomedicine, and combination product frameworks. The U.S. Food and Drug Administration (FDA) provides guidance through multiple documents: Botanical Drug Development (2016, updated 2023) emphasises characterisation of complex mixtures, batch-to-batch consistency, and mechanism-informed clinical development [10]. For nanotechnology-enabled products, the FDA's Considering Whether an FDA-Regulated Product Involves the Application of Nanotechnology (2022) and Drug Products, Including Biological Products, that Contain Nanomaterials (2024) outline expectations for physicochemical characterisation, in vitro/in vivo correlation, and risk-based safety assessment [11]. Critically, the agency encourages early engagement via pre-IND meetings to align on CMC (chemistry, manufacturing, and controls) strategies for complex phyto-nano systems [12].

The European Medicines Agency (EMA) offers complementary guidance through its Reflection paper on nanotechnology-based medicinal products for human use (2023) and Guideline on the quality of herbal medicinal products (2024 update) [13,14]. EMA emphasises a "quality by design" (QbD) approach, requiring detailed justification of nanocarrier selection, demonstration of colloidal stability under physiological conditions, and assessment of potential interactions between phytochemicals and nanomaterial components [15]. Both agencies stress the importance of robust analytical methods for quantifying active constituents in complex matrices, with EMA specifically recommending orthogonal techniques (e.g., HPLC-MS/MS combined with NMR or cryo-TEM) to verify identity, purity, and loading efficiency [16]. For combination products (e.g., phyto-nanoparticles + biologics), regulatory classification depends on the primary mode of action, necessitating coordinated review between drug and device/biologics divisions [17]. Harmonisation efforts through ICH (e.g., Q3D on elemental impurities, M7 on mutagenic impurities) further support global development, though region-specific requirements for traditional medicine evidence (e.g., EMA's HMPC assessments) may influence submission strategies [18].

9. Future Perspectives and Research Gaps:

Despite remarkable progress in phytotherapeutic and advanced drug delivery research for UC, several critical knowledge gaps and translational barriers must be addressed to realize sustained clinical impact. First, the lack of standardized botanical characterization and batch-to-batch reproducibility remains a primary impediment to regulatory approval and meta-analytic validation. Future studies must implement harmonized chemometric profiling, DNA barcoding, and pharmacopeial monographs to ensure consistent phytochemical potency across manufacturing sites. Second, while preclinical models demonstrate promising efficacy, most human trials are underpowered, short-duration, and lack placebo-controlled, double-blind rigor with validated endoscopic and histological endpoints. Multicenter, phase III randomized controlled trials incorporating mechanistic biomarkers (e.g., fecal calprotectin, mucosal transcriptomics, and microbiome metabolomics) are essential to establish dose-response relationships and long-term remission durability.

Third, the pharmacokinetic and pharmacodynamic interplay between engineered nanocarriers, phytochemicals, and the dysbiotic UC microbiome remains poorly characterized. Advanced in silico modeling, organ-on-a-chip platforms, and patient-derived intestinal organoids should be leveraged to predict colonic release kinetics, microbiota-mediated biotransformation, and host immune crosstalk. Fourth, regulatory frameworks globally lack unified pathways for complex hybrid formulations that combine botanicals, nanomaterials, and biologics. Harmonization of FDA, EMA, and ICH guidelines through a “Quality by Design” (QbD) paradigm, coupled with

real-world pharmacovigilance databases, will streamline clinical translation and post-marketing safety monitoring.

Finally, the integration of artificial intelligence and machine learning in formulation design offers unprecedented opportunities for optimizing carrier composition, predicting patient-specific responsiveness, and accelerating scale-up manufacturing. Future research must prioritize personalized therapeutic strategies informed by pharmacogenomic profiling, microbiome stratification, and disease phenotyping. Addressing these gaps will transform integrative UC therapeutics from experimental concepts into precision medicine standards, ultimately improving patient outcomes and healthcare sustainability.

10. CONCLUSION:

UC remains a complex, multifactorial disease that continues to challenge conventional therapeutic paradigms. While aminosalicylates, corticosteroids, and biologics form the cornerstone of current management, their limitations in efficacy, safety, and cost necessitate innovative, patient-centered alternatives. Phytotherapy offers a compelling multi-target approach, leveraging anti-inflammatory, antioxidant, immunomodulatory, and microbiome-modulating properties deeply rooted in traditional medicine and increasingly validated by contemporary science. However, inherent pharmacokinetic barriers, phytochemical variability, and inadequate clinical standardization have historically constrained its widespread adoption.

The emergence of advanced non-herbal novel drug delivery systems—including polymeric and lipid nanoparticles, vesicular carriers, stimuli-responsive hydrogels, and microbiota-triggered platforms—has fundamentally transformed the therapeutic landscape. These engineered systems overcome bioavailability limitations, enable site-specific colonic delivery, protect labile compounds from degradation, and facilitate synergistic hybrid formulations that combine botanicals with conventional or biologic agents. Preclinical and emerging clinical evidence consistently demonstrate superior mucosal healing, reduced systemic toxicity, and enhanced patient compliance compared to traditional oral regimens.

Nevertheless, successful clinical translation demands rigorous standardization, robust multicenter trials, harmonized regulatory pathways, and comprehensive long-term safety profiling. By integrating ethnopharmacological wisdom with cutting-edge pharmaceutical engineering, systems biology, and precision medicine, the next generation of UC therapeutics holds immense promise. Ultimately, this integrative paradigm will not only advance mucosal healing and remission maintenance but also establish a sustainable, mechanistically grounded model for managing chronic IBD.

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