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REVIEW ARTICLE

A systematic review of nano formulation of natural products for the treatment of inflammatory bowel disease: drug delivery and pharmacological targets

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Abstract

Inflammatory bowel diseases (IBD), which is classified into Crohn's disease and ulcerative colitis, are among chronic gastrointestinal diseases with unknown pathogenesis. Diverse strategies have been applied for the treatment of this chronic disease. However, selective and site-specific routes of drug delivery to the inflamed location of the colon remain of high importance. Consequently, the application and effects of natural products in the form of nanoformulation and stimuli responsive nanoparticles as a novel strategy for the treatment of IBD are discussed in this review article. This approach may potentially overcome some complications that are associated with conventional means of colon drug delivery. Meanwhile, in vitro and in vivo studies pave the way for understanding of the mechanism that lies behind this chronic relapsing disease and potentially more effective treatment.

Keywords Inflammatory bowel disease · Natural nanoformulation · Stimuli responsive nanoparticles · Crohn's disease · Ulcerative colitis

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Introduction

Inflammatory bowel disease (IBD), which affects millions of people all over the world, is a chronic, recurrent-remitting inflammation of the small intestine and colon that comprises ulcerative colitis (UC) and Crohn's disease (CD). (1, 2) It is typified by periodic abdominal pain, vomiting, fever, bloody stool, diarrhea and weight loss, which can affect quality of life and enhance risk of colorectal cancer. (3, 4) Although the etiology of IBD is not completely understood, recent studies have shown that it is likely influenced by the interaction of environmental, genetic, and immunological factors. (5) Disturbance in synthesis and release of anti-inflammatory cytokines, including interleukin (IL)-4, IL-10, and IL-11 or transforming growth factor (TGF)-β, as well as pro-inflammatory cytokines, such as tumor necrosis factor α (TNF-α), interferon γ (IFN-γ), IL-1β, IL-6, and IL-12, and an extreme production of reactive oxygen species (ROS) results in tissue damage which may play a pivotal role in the intestinal inflammation (4, 6, 7).

The conventional therapeutic strategies for treatment of IBD include application of anti-inflammatory drugs such as aminosalicylates, immunosuppressants, biological agents, and corticosteroids. However, these medications result in several side effects, such as allergic reactions, diarrhea, nausea, lymphopenia, and pancreatitis, which are mainly because of their systemic absorption. (1, 8) These facts have led to efforts in the development of therapeutic strategies that may be safer and more effective in the management and treatment of IBD. (4, 5, 9)

Natural products may be a hopeful source of new therapeutic agents in IBD. Several studies reported that phytochemicals, such as phenolic compounds and flavonoids, possess anti-inflammatory and antioxidant activity, which modulate various inflammatory mediators, such as TNF-α, IL-1β, IL-10, IL-6, inducible nitric oxide (NO) synthase (iNOS), prostaglandin E2 (PGE-2), and cyclooxygenase (COX)2. (8, 10). Conventional administration of natural drugs is limited by low solubility, permeability, and bioavailability. To overcome these challenges, nanonization and micronization may be a suitable strategy to improve the physicochemical properties of the drugs. (11)

Natural and synthetic nanoparticles and microparticles, such as nanovesicles, liposomes, exosome-like nanoparticles, and micelles, improve bioavailability, stability, specificity, and biodistribution of natural products. (12) In addition to nano-sized and microsized drug delivery systems, specific delivery of medications to the inflamed areas of the intestinal tissue can increase the local concentration of the drugs and significantly reduce adverse effects caused by systemic absorption of drugs. (1, 6, 12) Therefore, natural nanoformulations have attracted the attention of investigators for further extensive research. The purpose of this current study is to review nanoformulation of natural products and discuss their mechanisms of actions for the treatment of IBD.

Description of study selection

Electronic databases, including "PubMed", "Cochrane" and "Scopus," were searched with the keywords "inflammatory bowel disease" or "colitis" in title/abstract along with "plant," "herb," "phytochemical," "flavonoid," or "polyphenol" in the full text. The term "nano" was excluded in the search due to the probability of exempting special methods and materials. Data was collected until January 2018 with a focus only on English language articles. Primary results were evaluated by two investigators. Articles regarding the in vivo and in vitro models of IBD were selected. From a total number of 2490 articles, 397 were excluded due to duplicated results, 10 were excluded because they were reviews, and 2047 were irrelevant based on title and/or abstract information. From 36 retrieved articles, 6 were excluded because of their full text and finally a total number of 30 articles were included in this review, as shown in a summary of results in Fig. 1.

Conventional vs nanoformulation therapies

Conventional options for the treatment of IBD have been utilizing anti-inflammatory medications like salicylates, steroids, or immunosuppressants. (13, 14) Although these medications are efficient, their nonspecific actions on the immune system leads to short- and long-term side effects such as nausea, elevated liver enzymes, allergic reactions, and pancreatitis. On the other hand, sustained drug release platforms, such as capsules, tablets, and pellets, are designed for long-term targeted drug delivery to the colon. However, they are not applicable in all types of IBD patients and their efficacy is still under question. (8)

Targeted therapy based on the pathophysiology of inflammatory response in IBD is a recent advance, which is divided into three strategies: fabrication of inhibitors of inflammatory cytokines including TNF-α that results in T lymphocyte apoptosis, recognition of anti-inflammatory cytokines that downregulate T lymphocyte proliferation, and synthesis of selective adhesion molecule inhibitors which suppress T lymphocyte transport into the gut epithelium. (8, 15) Studies have shown that anti-TNF-α agents are the most promising anti-colitis agents in the market. However, this agent must be administered systemically and its application is limited by significant side effects. Therefore, a suitable carrier system for targeted and specific drug delivery to the colon is required. (8, 15) The most relevant nanoformulation method used for colon delivery is the application of stimuli responsive nanoformulations, which will be discussed in detail in the next sections.

Stimuli responsive nanoparticles of natural products for drug delivery of colon

Nanotechnology has greatly impacted diverse fields of science and research areas, and has made significant advances in the field of pharmaceuticals and drug delivery. (10, 16–18) Several types of modifications can be applied due to the nature of nanoparticles. The physical and chemical characteristics of polymers form stimuli responsive structures and the effects of controlled release of their encapsulated contents are currently being investigated. The stimuli are commonly classified into two groups: internal stimuli; including redox potential, endolysosomal pH, and enzymatic activities; and external physical stimuli including light, temperature, electric field, ultrasound and mechanical force. (18) Acheiving the proper response can be obtained through introduction of chemical groups into the polymer structure. The synthesized

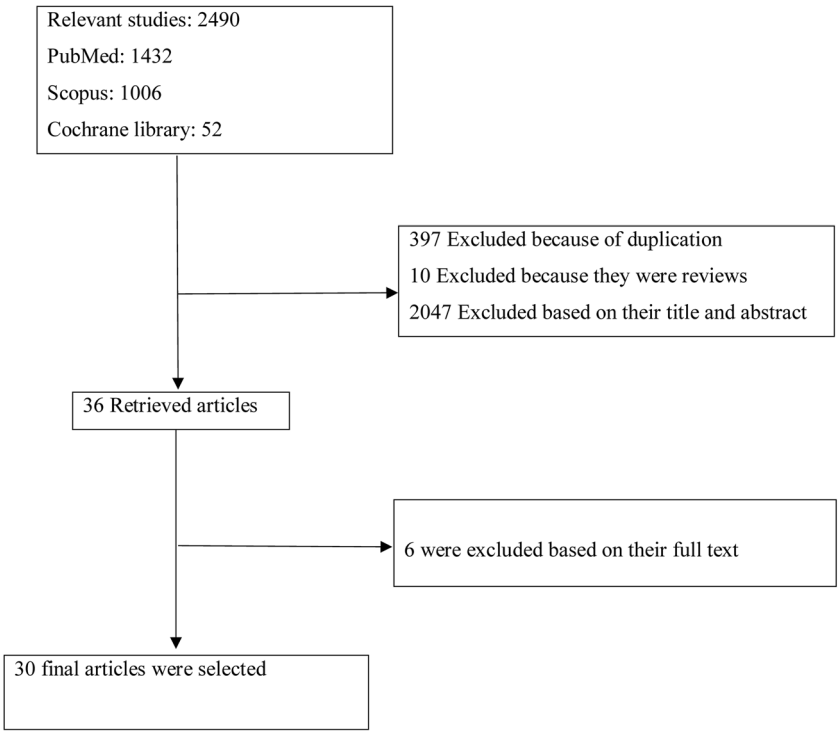

Fig. 1 Diagram of search in different databases and the results

conformations are capable of chemical and physical changes including bond cleavage, swelling, membrane fusion, and disassembly in response to precise stimuli that subsequently result in structure disruption and release of contents. In the following section, recent progress in stimuli-responsive nanostructures for delivery of natural compounds to the colon region is investigated as well as the advantages and disadvantages of different strategies for the biomedical applications.

pH-sensitive systems

pH-sensitive systems are a desirable approach in understanding controlled drug delivery to the gastrointestinal tract (GIT). (19) The pH-responsive property is based on polymers with acidic or basic groups that can exchange protons depending on the varying ranges of pH along the GIT. Different pH-sensitive polymers have been used for drug delivery in treatment of IBD. Eudragit S 100 (ERS 100) is a biocompatible polymer for colon-specific drug delivery that is accepted for oral administration and is certified in the USA, Europe, and Japan. (20) ERS 100 dissolves in aqueous solution of pH 6–7 and releases its products in the colon. Makhlof et al.[19] reported that ERS 100 MPs releases its cargo in the upper GIT, where the pH shifts from higher to neutral pH. Poly(lactide-co-glycolide) acid (PLGA) is a biocompatible, biodegradable, and permeable hydrophobic polyester polymer with FDA approval for biomedical and drug delivery applications. (21–23) Bo Xiao et al. (24) incorporated pH-sensitive Eudragit S100 (ERS100)/PLGA microparticles (MPs) for the sustained delivery of curcumin to the colon. In this study, ERS 100/PLGA MPs, with a particle size range of 1.5 to 1.9 μm, were synthesized, and the drug was loaded with a slight addition of PLGA to the system. This system may be utilized as a model for controlled and efficient delivery of curcumin to the damaged colon tissues. (24) In another study by Ana Beloqui et al. (25), the combination of both pH-sensitive PLGA and polymethacrylate polymer (ERS 100) loaded curcumin nanoparticles (NPs) were evaluated. Curcumin NPs were encapsulated in polymeric pH-sensitive NPs and the selective delivery of curcumin to the inflamed mucosa was investigated. The curcumin nanoparticle diameter was achieved at 166 ± 3 nm. This indicated that curcumin NPs presented appropriate physicochemical properties, such as size and surface charge for colonic drug delivery. Curcumin NPs were successfully able to cross the epithelial barriers of Caco-2 cells. Moreover, TNF-α secretion in pre-treated LPS-activated macrophages was remarkably reduced upon the use of curcumin NPs. Furthermore, the in vivo study in dextran-sulfate (DSS)-induced colitis model in mice showed notable decrease in myeloperoxidase (MPO) activity and TNF-α secretion after 8 days of administration, demonstrating successful colonic delivery of curcumin. (25) Gugulothu et al. (26) formulated a system based on ERS100 NPs loaded with a combination of curcumin-celecoxib NPs. pH-sensitive NPs of curcumin-celecoxib with a particle size of less than 111 ± 0.55 nm demonstrated successful delivery of their cargo in the distinct pH of colon. (26) In another study by Ali et al. (27), budesonide, a synthetic glucocorticoid with an anti-

inflammatory effect, was encapsulated in PLGA nanoparticles via oil in water (O/W) emulsion technique. The same authors mentioned that formulation was further coated with methyl-methacrylate-copolymer, a pH-sensitive polymer. Both of the formulations were examined and the results show that pH-sensitive coated polymers release their cargo in response to neutral rather than alkaline pH; therefore, averting premature and quick drug release. These results confirm the potential application of polymeric nanocarriers for targeted drug delivery to intestinal tissue via oral administration. (27)

Enzyme-sensitive system

Enzyme-mediated drug delivery occurs in the presence of specific enzymes including proteases, phospholipases, and glycosidases, which are dominant in pathological conditions, such as inflammation or cancer. With targeting, a polymeric structure that is susceptible to a specific enzyme, undergoes the cleavage process at the target site, leading the cargo to be released and its specific function to take place (28). Regarding this strategy, Castangia et al. (29) investigated the enzyme-sensitive and prebiotic complex of chitosan/nutriose polymer, which represented a promising procedure for oral delivery of quercetin (3,3′,4′,5,7-pentahydroxyflavone). Quercetin is a common flavonoid found in nature and a potential antioxidant and anti-inflammatory agent for the treatment of IBD in the colon. Chitosan is the most broadly used polymer for coatings of phospholipids and a mucoadhesive polysaccharide that is soluble at gastric pH 2, but is insoluble at a pH of 5.5 in the small intestine. However, regarding to the solubility of chitosan, it cannot be used alone to retain its structure in an acidic environment. In this work, Quercetin-loaded polyethylene glycol (PEG) vesicles were coated with chitosan. Nutriose, a water soluble branched dextrin with high levels of fiber content, was added to the chitosan and the phospholipid vesicle with polysaccharide–starch complex formulation containing qurcetin was obtained. The total size of this system was 132 ± 6 nm. The chitosan-nutriose complex was less soluble than single polymers in the gastrointestinal fluids at pH 2–7, but was still susceptible to enzymatic degradation in the colon. Chitosan and nutriose have an inclination for hydrolysis into single monomers in the presence of colon enzymes. Furthermore, nutriose hydrolyzation products have been used as nutrients for endogenous microflora, which may proliferate and facilitate the reconstruction of physiological conditions in impaired tissue. Consequently, this system may be used for both prevention and treatment of chronic intestinal inflammation (29).

Redox-sensitive nanoparticles

The colonic bacterial azo reduction is one method of targeted drug delivery to the colon in the form of polymeric coatings, prodrug, and matrices. (30) A well-known example of azo reduction is the prodrug sulfasalazine, which releases 5-aminosalicylic acid (5-ASA) in response to azo reduction in the gut and is considerably applied in the treatment of IBD. (31) In a recent study by Qiao et al. (32), an amphiphilic polycurcumin (PCur) composed of hydrophilic PEG and hydrophobic curcumin with disulfide, was designed in response to the bacterial reduction in colon. GSH was used to stimulate reduced levels in vitro condition. This nano particulate system possesses neutral surface charge that resulted in sedimentation of PCur in inflamed parts of colon and additionally enhanced the partition coefficient, which indicates smoothed transmembrane transport along with boosting oral bioavailability. The TEM and DLS results demonstrat the average particle size of 134.4 ± 4.2 nm. The in vivo and in vitro studies of PCur formulation demonstrat the physical and chemical characteristics to defeat barriers in the intestinal tissues to reach elevation in therapeutic efficiency. The ex vivo study was done in a solution of rat cecal content to simulate the real colonic environment for evaluating Cur release from the formulation. The results clarified that Cur release from PCur after incubation with rat cecal solution, was accelerated. Cur was inclined to decompose and release in the reducing environment including intestinal canal due to a redox sensitive disulfide bond, which is enclosed within the polymer chain of nanoformulation. This nanoformulation demonstrated a significant therapeutic system for treatment of inflamed colon tissues. (32) In another study by Sun et al. (33), an oral nanocarrier based on an amphiphilic polymer of inulin with 4-aminothiophenol (ATP) that is grafted onto carboxymethyl inulin (CMI) loaded with budesonide was developed. This amphiphilic formulation of inulin derivative (ATP-CMI) was successfully applied for specific delivery of budesonide to the inflamed colon tissue. The in vitro release of budesonide from ATP-CMI NPs demonstrated better selectivity in reaction to the reduced potential. Furthermore, in vivo experience illustrated that budesonide loaded ATP-CMI NPs is a superior choice for treatment of DSS-induced colitis in mice. This formulation accumulated in inflamed sites of the colon; disulfide bonds among ATP-CMI NPs and mucin resulted in the redox sensitivity release and boosted intracellular drug delivery. Therefore, this formulation is an advantageous strategy for oral drug delivery to the inflamed sites of colon. (33)

Natural nanoformulations for the treatment of IBD

Synthetic nanoparticles possess two significant problems. First, each part of the synthesized nanoparticles should be checked for possible in vivo toxicity prior to clinical applications. The second problem is limitations of production scale. Conversely, nanoparticles derived from natural sources are

believed to have lower toxicity and are significantly more secure and cost effective, which can overcome the aforementioned shortcomings of synthetic nanoparticles. (34) Natural products with anti-colitis actions can be classified into antioxidants, phytochemicals, dietary fibers, lipids, and microorganisms. Phytochemicals include polyphenols or flavonoids and are among the popular natural products with anti-colitis action. The anti-colitis effects of phytochemicals are present in their ability to modulate the levels of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and IL-6. In Fig. 2, different nanoformulations and their pharmaceutical advantages as anti-IBD agents is demonstrated.

Curcumin

Curcumin is a hydrophobic polyphenolic structure that is extracted from turmeric (*Curcuma longa* L.) rhizome and possesses innumerable biological and pharmacological characteristics, including anti-inflammatory, antioxidant, and anticarcinogenic activities. (10, 35) This compound has been widely studied in IBD and related disorders. In an experiment by Ohno et al. (36), curcumin nanoparticles were used to suppress the development of DSS-induced colitis in mice. Treatment with curcumin NPs notably decreased disease activity index and body weight loss. The production of nuclear factor κB (NF-κB) in colonic epithelial cells is also remarkably suppressed by curcumin NPs treatment. Curcumin NPs also improved the accumulation of butyrate-producing bacteria and the level of fecal butyrate. Furthermore, the increased expansion of $CD4^+$ $Foxp3^+$ regulatory T cells and CD103+ $CD8\alpha^-$ regulatory dendritic cells were observed. (36)

Silymarin

Silymarin is a complex of flavanolignans that is extracted from *Silybum marianum* and possesses potential intracellular antioxidant characteristics. Silymarin resulted in fixing of intracellular and surface thiols, and triggers antioxidant enzyme activity including glutathione peroxidase (GP_X), catalase, and superoxide dismutase. It possesses antiangiogenic property and impedes arachidonic acid. (37) Silymarin has membrane stabilization effect on hepatocytes and mast cells. It triggers the release of cytochrome C and activation of caspase-3 and 9, as well as segmentation of PARP. (38) It possesses intracellular antioxidant characteristic and impedes the induction of NF-κB in low concentrations and diminishes TNF-α, IL-1β, IL-6 levels, angiogenesis and COX. Selenium is an important element in a mammalian diet. It prevents the generation of ROS in mitochondria. It also decreases COX and intermediates of lipoxygenase hydroperoxidase; thus, selenium reduces the production of prostaglandins and leukotrienes. Selenium also suppresses LPS-induced NF-κB and MAP kinase and in doing so, relieves iNOS, inflammatory cytokines, and COX-2 gene expression (39, 40). In a study by Miroliaee et al. (41), the combination effect of selenium NPs and silymarin in decreasing NF-κB expression, oxidative stress biomarkers, and pro-inflammatory cytokines in rats with Trinitrobenzene sulfonic acid (TNBS)-induced colitis were investigated. Co-administration of silymarin and nano-Se (average size of 245 ± 82.47 nm) decreased NF-κB and showed a promising antioxidant profile, which is a potential candidate for treatment of IBD. (41) In another experiment by Varshosaz et al. (42), eudragit nanoparticles loaded with silybin were formed by means of solvent-evaporation emulsification method. The optimized nanoparticles size was 109 ± 6 nm with loading

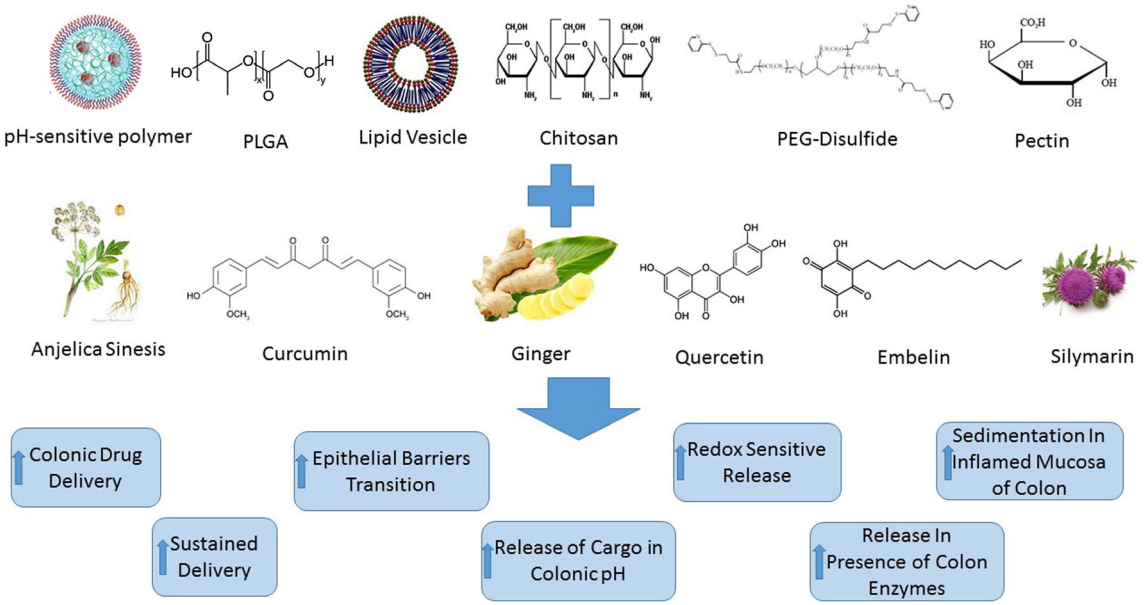

Fig. 2 Most relevant natural products-based nanoformulations and their pharmaceutical advantages as protective and therapeutic agents in IBD

efficiency of 98.3 ± 12% and release efficiency of 40.8 ± 5.5% at 24 h. Freeze-dried nanoparticles of silybin, blank NPs, dexamethasone, and normal saline were orally administered to animals with acetic acid-induced ulcerative colitis. The results demonstrated a significant reduction in TNF-α and IL-6 activity. (42)

Ginger-derived nanoparticles

Zhang et al. (3) assessed ginger-derived nanoparticles for the treatment of IBD. Ginger, the rhizome of *Zingiber officinale* Roscoe, is globally considered one of the most popular medicinal plants. Studies showed that ginger and its active components like 6-gingerol and 6-shogaol, possess anti-inflammatory, anti-oxidant, and anti-cancer activities (43, 44). Ginger was washed with water at room temperature. Afterwards, it was blended to extract juice, which was centrifuged to separate large ginger fibers. In the next step, the supernatant was ultracentrifuged. For the purification step of GSNPs, the suspension was transported to a nonstop sucrose gradient (8%, 30%, 45%, and 60% [g/v]) and then, ultracentrifuged to get bands between 8/30%, 30/45%, and 45/60% layers that were related to GDNP 1, GDNP 2, and GDNP 3 respectively, were selected. Ginger-derived nanoparticles with an average size of 230 nm, were delivered orally to the colon and did not generate any side effects. This natural product reduced the expression of TNF-α, IL-6, and IL-1β cytokines as well as elevated the expression of anti-inflammatory cytokines IL-10 and IL-1β. The results demonstrate that GDNPs can be massively produced and developed for treatment of IBD and colitis-associated cancer (CAC) (8). Zhang et al. (3), developed the novel siRNA delivery system based on edible ginger-derived lipid vehicles (GDLVs) for the treatment of ulcerative colitis. GDLVs were loaded with siRNA-CD98 (siRNA-CD98/GDLVs) and were orally administered to reach colon tissue and reduce the expression of CD98. Also, GDLVs possess outstanding biocompatibility at in vivo and in vitro condition. The authors recommended this system as a promising formulation for efficient siRNA delivery approach in consideration of limitations of synthetic nanoparticles for siRNA delivery. (3)

Quercetin

Among all flavonoids, quercetin (3,3′,4′,5,7-pentahydroxyflavone) is the most common flavonoid in the nature and significantly indicative of the subclasses of flavonol. (45) Quercetin possesses anti-inflammatory and anti-oxidant activity as well as advantageous effects on the intestinal inflammation via oral administration. (46, 47) In an experiment by Castangia et al. (29), PEG-coated vesicles composed of chitosan and nutriose-loaded quercetin were generated. Coated and uncoated vesicles were synthesized by employing soy phosphatidylcholine and quercetin. The in vitro release profile of quercetin at different pH ranges demonstrated PEG-coated chitosan/nutriose nanovesicles to be a suitable choice for colon drug delivery. These vesicles both improved and ameliorated symptoms of TNBS-induced colitis. (29)

Grape exosome-like nanoparticles

In a study by Ju et al. (48), grape exosome-like nanoparticles (GELNs) with the size of 380.5 ± 37.47 nm were introduced for the protection of colon against DSS-induced colitis. In this study, intestinal stem cells were targeted by GELNs which resulted in intestinal tissue remodeling and protection. GELNs were triggered by lipids and increased the proliferation of $Lgr5^+$ stem cells under physiological conditions. It was shown that only the Lgr5 intestinal stem cells resulted in better intestinal organoid structure than the in vitro condition. Liposome-like nanoparticles (LLNs) in cooperation with GELNs are needed for targeting the intestinal stem cells in vivo. The production of Lgr5+ stem cells was reduced via inhibition of the signaling pathway of ß-cantenin of GELNs-receiving cells. The GELNs system resulted in remodeling and modulation of the intestinal tissue renewal process. (48)

Embelin

Embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone) is a natural component that is derived from *Embelia ribes* Burm.f. Embelin possesses analgesic, anti-inflammatory, and antioxidant characteristics. (49) Embelin has been investigated for its advantageous effect in rats with DSS-induced colitis. (50) Embelin also has protective effects against acute ulcerative colitis, which is induced via acetic acid. (51) Badamaranahalli et al. (52) developed embelin-loaded lipid nanospheres with the size of 196.1 ± 3.57 to 269.2 ± 1.05 nm by means of liquid lipid soya bean oil (SBO)/virgin coconut oil (VCO) method. In vivo studies of acetic acid-induced ulcerative colitis in rats showed that embelin lipid nanospheres (LNs) therapy significantly decreased the levels of MPO, LDH, and LPO, and increased reduction in GSH levels that designated better treatment of UCs. (52)

Natural polysaccharides

Natural polysaccharides are used for colon drug delivery, since they are easy to work with, non-toxic, US FDA approved, and selectively degraded in the colon area. (53) Polysaccharides are mainly divided into plant and animal sources; each source is classified into different types. The most widely studied natural polysaccharides, including pectin, cellulose, chitosan, and dextran, are broadly utilized for developing colon-specific drug delivery systems. Polysaccharides are selectively degraded in the colon and protect the drug

formulation from premature release in the small intestine and stomach. Zhou et al. (54), presented polysaccharides of *Angelica sinesis* diels, a famous Chinese medicinal plant as a colon specific drug delivery system. This polysaccharide possesses an anti-inflammatory activity that inhibits neutrophil infiltration and gastrointestinal damage in rats. The angelica polysaccharide was used as a drug carrier and its monosaccharide, succinate, was used as a linker from which the dexamethasone polysaccharide conjugate was synthesized. This new polysaccharide conjugate is a successful colon-specific drug delivery system. (54) In another study by Li et al. (55), modified apple polysaccharides could potentially decrease the level of IL-22 and upregulate the expression of IL-22BP (55). Mechanisms of actions of natural nanoformulations in prevention and treatment of IBD are demonstrated in Fig. 3.

Kinetic challenges of pharmacotherapy in colon

Patients who suffer from IBD are 10 to 20 times more likely to contract bowel or colon cancer. Selective and specific drug delivery to inflamed colon tissues has received attention in the treatment of IBD due to the significant adverse effects of conventional therapies. Strategies for drug delivery include application of natural and synthetic nanoparticles along with stimulus responsive systems, which activate and release their cargo in response to endogenous or exogenous stimuli such as pH, enzyme, light, and magnetic field. Several factors like NPs size, shape, composition, charge, synthesis methods, administration routes (orally, intravenously), and degree of hindrance from immune system (macrophages, dendritic cells) influence drug delivery to the inflamed site of the colon. To achieve a better response, the drug delivery index for pharmacokinetic parameters of the drug is needed. These pharmacokinetic parameters can be determined by oral administration of single or multiple doses of colonic formulations. The main reason for the application of nanoformulations in IBD is to improve the pharmacokinetics and pharmacodynamics of the drug. Therapeutic response happens when the concentration of the drug is sufficient enough at the site of action to promote a desirable effect without causing toxicity. Therapeutic index is another parameter that indicates the effective and toxic doses of drugs; this concentration range can be achieved when the drug formulation suitably passes physiological barriers and releases its cargo at the specific target site. (56) Nanoparticles possess many characteristics that can overcome the problems of conventional drug delivery, such as passage through biological barriers, suitable entrance into the cell, and controlled and sustained release of their cargo. Because of the small size of the NPs, they can boost luminal residence time, and the adhesion and penetration to the mucosa can be drastically enhanced. (21, 57, 58) Another factor that results in adhesion to the mucosa is the Brownian motions of the suspended NPs in the luminal content. (59, 60) Furthermore, the small size of the NPs on its own can increase the endocytosis of nanoparticles with a size smaller than 100 nm and transcytosis process in nanoparticles smaller than 500 nm. (61, 62) In IBD and its inflammatory condition, the intestinal epithelial line undergoes malfunction and loses its integrity; therefore, NPs can greatly penetrate into the mucosa and enhance retention time. (21, 61) However, the presence of unique properties of NPs have led to unpredictable toxicological data produced from even in-vitro models. Therefore, unique characteristics of NPs including optical features,

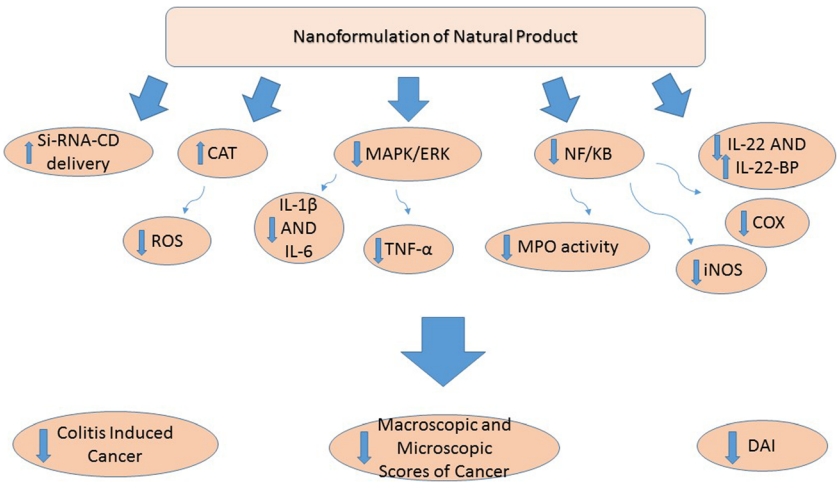

Fig. 3 Mechanisms of actions of nanoformulation of natural products in IBD. **Abbreviations:** CAT, catalase; ROS, reactive oxygen species; MAPK/ERK, mitogen-activated protein kinases/extracellular signal-regulated kinases; IL-1β AND IL-6, interleukin-1β and interleukin-6; TNF-α, tumor necrosis factor-α; NF/κB, nuclear factor-κB; MPO activity, myeloperoxidase activity; COX, cyclooxygenase; iNOS, inducible nitric oxide (NO) synthase; DAI, disease activity index

surface charge, changes in pH, dissolution, and other properties, can even interfere with detection systems and result in unknown toxicological effects harmful to both human and habitat. (63) The NPs ADME (Adsorption, Distribution, Metabolism and Excretion) characteristics including distriburation rate, internalization through biological barriers, and cellular uptake, can be influenced by toxicity and may cause other toxic effects to the central nervous system, kidney, spleen, and other body organs. The nanopharmaceutical cytotoxicity procedures are not clearly described, but ROS formation, upregulation of transcription factors, DNA damage, mutation, and alteration in GSH/GSSG ratio are among the main cytotoxicity mechanisms. (64) The most common event after exposure to nanoparticles in the cell system, is the generation of ROS. ROS generation leads to activation of diverse pathways that are dependent on the applied nanomaterials. The nanoparticle-induced toxicities affect the concentrations of metallothionein (MT), superoxide dismutase 2 (SOD2), and existing of heme oxygenase-1 (HMOX 1). In addition to ROS generation, adverse outcomes (AOs), such as apoptosis, inflammatory responces, mitochondrial damage, cell cycle arrest, or a mixture of effects have also been mentioned. Inflammatory response measured via cytokine expression is not a common route for screening and includes interluekin-8 (IL8), interleukin-6 (IL6), interleukin-1beta (IL1β), tumor necrosis factor-alpha (TNFα), macrophage inflammatory protein-1alpha (MIP1α), interferon gamma (IFNγ), monocyte chemotactic protein-1 (MCP1), and intercellular adhesion molecule-1 (sICAM1) regulation upon activation of normal T cell expressed and secreted (RANTES) biomarkers. (65) Therefore, for safety assessment and efficacy of administrated nanodrugs, an accepted animal model or approved primary cell culture is highly recommended to examine all aspects of safety of nanodrugs for therapeutic applications. (66) Different types of drugs that have been used for treatment of UC and CD patients include anti-CD20 (rituximab), new anti-TNF drugs (adalimumab, pegol, certolizumab, onercept, etanercept and golimumab), anti-α4 integrins (natalizumab and vedolizumab), and T cell inhibitors (abatacept). While these drugs demonstrate great therapeutic effects and tolerance, the aforementioned complications in application should still be considered. (9)

Conclusion

In recent years, the development and application of nanotechnology has significantly impacted the field of drug delivery systems. The use of many natural metabolites or analogues are a potentially successful strategy for the search of new therapeutic agents against human diseases. Unfortunately, the pharmacological application of potentially active natural compounds in clinical trials has been limited due to their *low* oral *bioavailability*. In this review, the development and application of nanoparticles derived from natural compounds in a drug delivery system represent a major alternative approach to increasing treatment effectiveness of inflammatory human bowel disease. Nanoparticles are a useful alternative to enhance the *bioavailability* of natural compounds, both in vitro and in vivo investigations. Studies have shown that nanotechnology has the ability to deliver effective therapeutic agents to specific areas of the body, such as the colon, and control the release of natural bioactive metabolites. The purpose of nanoformulation is to create a reliable system that can encompass all the advantages of efficient delivery with a unique formulation. Advancements in the development of nanotechnology may improve achievement of higher concentrations of natural products, leading to *higher* intracellular drug *concentration and improvement of effectiveness* of *natural* agents in many human *conditions, such as IBD.* This preliminary nanoformulation system should behave consistently in case of alterations in gastro-luminal pH and enzyme profile in the colon environment as well as demonstrate optimal release profile regardless of immediate changes. Conventional routes of colon drug delivery, such as oral and IV administration are popular methods of treatment, but they cause some systemic complications, which have been lessened in the form of colon specific nanoformulation drug delivery. Thus, targeted delivery compounds in nanoformulations could be used to reduce side effects of IBD by acting in specific damaged areas and limiting potential toxicity. However, effective targeting remains a challenging issue that must be overcome with further studies. Nanoformulations are a novel method of drug administration because they are easy to manipulate, US FDA approved, nontoxic, and selectively and specifically degraded in the colon region. These qualities are promising materials for application in a colon specific drug delivery system. Researcher efforts in the advancement and development of nanoformulations have contributed significantly to the treatment of IBD as well as improvement of alternative treatments that were discussed in this review. Ultimately, this may lead to the prospect of stable and prolonged remissions in patients with reduced drug consumption.

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