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Review Article

IMPORTANCE OF NANOCARRIERS AND PROBIOTICS IN THE TREATMENT OF ULCERATIVE COLITIS

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ABSTRACT

Ulcerative colitis (UC) is an inflammatory chronic disease primarily affecting the colonic mucosa; the extent and severity of colon involvement are variable. Ulcerative colitis is identified by mucus diarrhea, tenesmus, bowel distension, and anemia. 5-aminosalicylic acid drugs, steroids, and immune suppressants are used for the therapy of ulcerative colitis. The mainchallenges in the management of thediseaseare drug-related side-effects and local targeting. To overcome these challengesprobiotics and micro and Nanoparticulate system0Tauspiciousapproaches to overcome drug-related adverse side effects and local targeting.Upon ingestion, the probiotics can result in beneficial health effects. Probiotics and micro and nanoparticulate approaches for suitable targeting and overcome the drug-associated side effect. Probiotics are mainly used as gut modulators but are also nowadays explored for their use in ulcerative colitis.The current therapeutic goals are to achieve clinical remission along with mucosal healing, avoidance of complications such as side effects of the drug and to improve the quality of life. The use of probiotics to increase the health of the intestine and used to block or manage intestinal disorders. They may prevent the induction of inflammatory reactions. Probiotics must be inspected for efficacy in the prevention and management of a wide spectrum of gastrointestinal diseases, like antibiotic-associated diarrhea.Micro and Nanoparticulate drug delivery system has been achieving huge importance for targeting of the drug to colon locally at a controlled and sustained rate.

Keywords: Inflammatory chronic disease, Probiotics, Micro and Nanoparticulate

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INTRODUCTION

IBD is a disease of the gastrointestinal tract and it isidentified by unrestricted inflammation caused by unsuitable and constant activation of the mucosal immune system.Ulcerative colitis and Crohn'sdisease are the different types of inflammatory bowel disease (IBD), which are very common, with associated significant morbidity and mortality [1,2]. While the main reasons are mostly undetermined of thepathogenesis of IBD but the factors related to the environment and genetic vulnerability are found to be associated with it[3].Ulcerative colitis is chronic inflammatory disorders found in the intestinal tract that causes the life-threatening issue and have an increasing occurrence worldwide [4]. The small intestine and large intestine or colon are the major areas involved in the IBD, which are manifested by the persistent inflammation in certain areas of the mucosa[5]. It is determined by intermittent rectal bleeding, diarrhoea, rectal urgency, andtenesmus[6]. Molodecky*et al.* (2010) studied In Western Europe, Asia, and North America;this disease has an annual occurrence of approximately 24.3 per 100,000 populations every year, 6.3 per 100,000 per year, and 19.2 per 100,000 populations every year, respectively.IBD is becoming a world disorder because of its increasing occurrence and prevalence of it concerning time. There is a very lower occurrence in Africa, South America, and Asia[7]. It has been predicted that more than 1 million individuals suffered from IBD intheUS, out of which 100,000 are children. IBD is in 5th rank amid the most common gastrointestinal disorder.

Epidemiology

The occurrence and prevalence of ulcerative colitis have been expanding over time worldwide. Ulcerative colitis is mainly relatedto recurrent attacks with complete remission of symptoms. Kim *et al.* (2017) studied shownthe increased incidence of the disease is more (three to six-fold more) in Jewish and it is more common in Caucasians than in black. In Western Europe occurrence of approximately 6 to 8 cases per 100,000 populations and the USA, and an estimated occurrence of about 70 to 150 per 100,000 populations. Within Europe, it seems a variance in ulcerative colitis incidence; with the eastern countries have low incidence than in western and in northern countries. The possibility of progression of ulcerative colitis in children of animmigrantfrom low-occurrence to high-occurrence state is the same as non-immigrants. In the world, IBD is becoming a big problem because of its increasing occurrence and widespread of itsconcern for time. Theincidence in Africa, Asia, and South America is very low[8,9]. In the United States, it has been predicted that 100,000 children are affected by IBD in theUS out of 1 million people.

Etiology of ulcerative colitis

The precise cause of ulcerative colitis is not known, but some factors that are related to the disease, including family history, use of oral contraceptives, genetic, Gut/environmental, psychosomatic, autoimmune, epidemiological are responsible.An autoimmune condition stimulated by colonic bacteria resulting in inflammation of the gastrointestinal tract is possibly called Ulcerative colitis.Family history is there in around25-40%of children; the people about to wth concerning anindividual with Chrons disease are 17-35 times more likely to develop ulcerative colitis than the general population. A combination of factors, including abnormal mucosal immune responses, intestinal epithelial dysfunction, and defects of host interactions with intestinal microbes, can contribute to CD[10]. Environmental factors consist of immune interactions, bacterial infections, and epithelial barrier functions. Epidemiological studies consist of nutritional behavior, smoking habits, ingestion of drugs, hormonal conditions, variations resulting from different climates, and changes due to social conditions. Hygiene theory suggests that the decline in enteric infections in developed countries has caused insufficient progress of the dictatorial processes that mucosal immune responses are bound[11].The inflammatory factors can be investigated through different cell signal pathways, inflammatory mediators such as tumor necrosis factor α (TNF-α), Interleukin-6, Interleukin-1, Interleukin-4, Interleukin-12, Interleukin-11 and Interleukin-4, and Eicosanoids profiles[12].

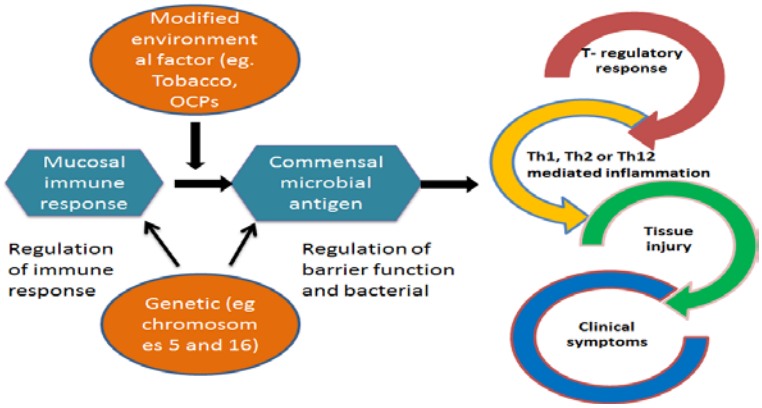

Fig.1: Etiologic factors in IBD

Fig. 1[13] shows the etiologic factors in IBD. Chronic inflammation resulted from the production of reactive oxygen species produces dysplasia, which can turn into CAC, i.e., colitis-associated colorectal cancer, which is a critical type of ulcerative colitis. Therefore, with ulcerative colitis, the high possibility of colon cancer in patients is there[14]. The mucosal layer of the colon is the region where the inflammation is confined. The rectum is always involved, with inflammation expended proximally in a confluent fashion.In opposition, theCD is not limited to a restricted region and can be found in any part of GIT, and the inflammation can be asymmetrical, transmural, and segmented[15].

Pathophysiology of ulcerative colitis

Pathogenesis of ulcerative colitis remains unknown, in current years several some many findings conclusion point to an over incentive or insufficient regulation of the mucosal immune system as a crucial pathophysiologic pathway, and then particular emphasis can be given to the analyses of immunologic reactionsormucosal inflammation. Several factors of ulcerative colitis that result in primary immunological disorders or there are doesn't appropriate pathological immunological reactions to an environment e. g, commensal intestinal microorganisms. The first main cause is the deregulation of the immune system, which resultsinuncontrolledimmune responses to usual microflora.

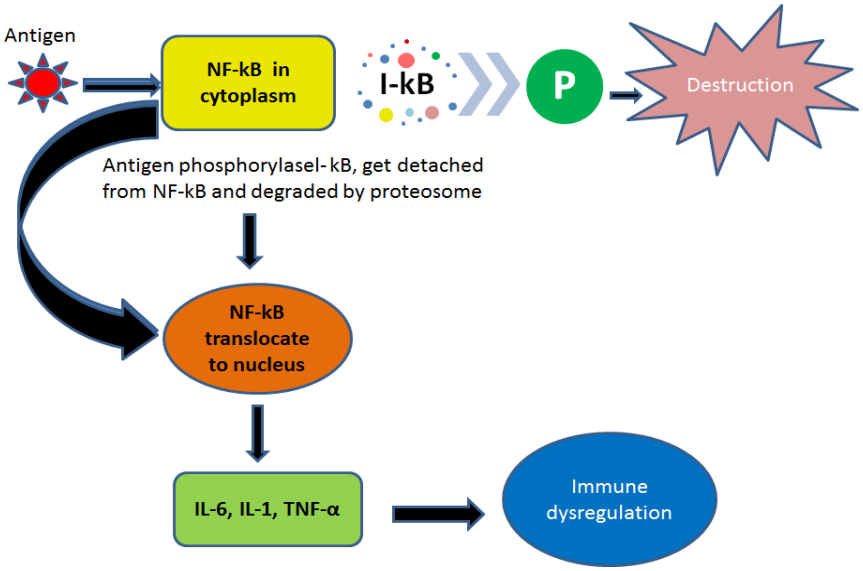

Fig.2: Mechanism of UC via the NF-κB mechanism

In maximum (i.e. 95%) cases, deregulations of the immune system expend directly from the rectum in a continuous pattern involving part or every part of the colon. A second cause is the epithelial cell abnormalities and alters in the content of gut microflora that facilitates an unusual mucosal immune response[16]. A third cause is reducedgene expression i.e., alteration of the gene that is CARD15/NOD2[17].Ulcerative colitis is a chronic condition that contains large intestine and colon, where the entire organ or a portion of the gastrointestinal is affected by inflammation. Ulcerative Colitis is the inflammatory bowel disease which continualinflammation and ulceration which expend from the rectum towards the caecum and is normallyrelated to extra IL-13 producing where, Crohn's disease is related tothe abundant production of IL-12/IL-23 and IFN-γ/IL-17, it usually involves part of ileum and colon where discontinuous ulceration and inflammation including granulomas occurs [18]. Fig. 2[19] shows the mechanism of UC by NF-Kbmechanism. Unusually increased intestinal permeability is oneof the factors that caused ulcerative colitis and that will result in disease continuation, which can be reported by some authors. Thus breaking down the barrier function of epithelial wall conduct to increase the permeability of mucosa for luminal antigens, bacteria or microorganisms, and loss of water and electrolytes by activating the inflammatory process.Due to breakage of the barrierfrom the epitheliumwater,and various electrolytes have been lost Incorporation of this, the lost polarity of damaged intestinal cells that results in apical expression of the transferrin receptor protein, whose appearance is mainly increasedon apical

and basolateral sites of enterocytes in the inflamed mucosa of IBD patients.

Signs and symptoms of ulcerative colitis

The main symptoms of ulcerative colitis (UC) includepain, discomfort and diarrhea with blood(table 1). Fever and weight loss occursometimes.Extraintestinal symptoms can be an initial expression or can occur subsequently in the duration of the illness. In proctitis, occasionally, obstipation can be the initial symptom.Weight loss, tachycardia, rectal bleeding, and bowel inflation are significantsymptoms. Ulcerative colitis is divided into various classes i.e.,distal, extensive,ulcerativeproctitis. Meier *et al.* (2011) have studied which briefly explains that ulcerative colitis is given in fig. 3 [20]. Around eighty percent of the patients suffer from proctitis, and extensive colitis is found in 20% of patients.

Table1: Initial symptoms of ulcerative colitis

S. No.	Symptoms	% frequency	Referances
1.	Diarrhoea	96.4 %	[20]
2.	Blood in stool	89.3 %	[20]
3.	Pain	81.3 %	[20]
4.	Generally unwell	40.2 %	[20]
5.	Arthralgia	27.7 %	[20]
6.	Fever	20.5 %	[20]
7.	Weight Loss	38.4 %	[20]
8.	Fever	20.5 %	[20]
9.	Skin Changes	20.5 %	[20]
10.	Loss of appetite	15.2 %	[20]
11.	Ophtalmopathies	7.1 %	[20]
12.	Nausea	6.3 %	[20]

However,proximal extension results late in around 50% of patients with proctosigmoiditis, and in otherpatients, the opposite occurs. A change in the area of the disorder should arise new symptoms. The duration of the disease can change.

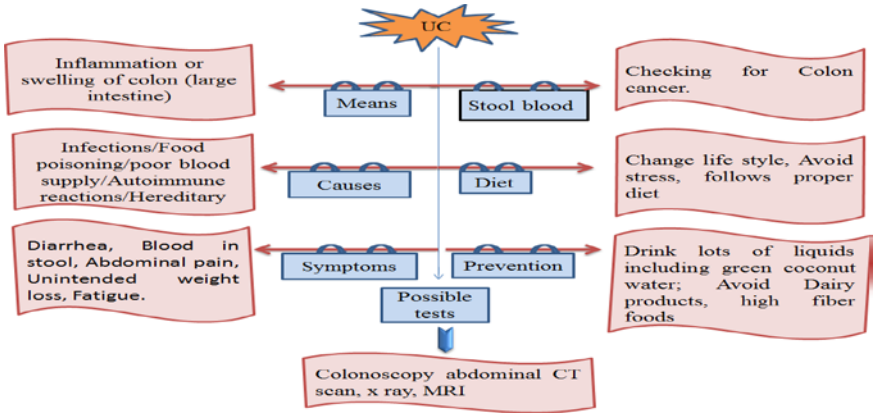

Fig.3: A schematic diagram for ulcerative colitis

Table 2: Drugs used in the treatment of ulcerative colitis

Drug type	Drug name	Available routes	Efficacy	Induction dose	Maintenance dose	Adverse events	References
5-Amino Salycilate	Mesalamine Balsalazide Sulfasalazine	Oral Rectal	Induction and maintenance	Mesalamine: 2-4.8g(oral) Mesalamine: 4g(enema) Mesalamine: 1g(suppository) Balsalazide: 6.75g Sulfasalazine: 2-4 g	Mesalamine: 1.6-2.4 g Mesalamine: 4 g (enema) Mesalamine: 1g (suppository) Balsalazide: 6.75g Sulfasalazine: 2-4 g	Headache, nausea, diarrhea, interstitial nephritis,leukopenia, and hepatitis	[22,23]
Corticosteroids	Prednisone Budesonide Methylprednisolone	Oral Rectal IV	Induction only	Prednisone: 40-60 mg Budesonide: 9 mg Methylprednisolone: 40-60 mg daily		delirium, cataracts, glaucoma, striae, delayed wound healing,adrenalinsufficiency	[22,23]
Thiopurines	Azathioprine Mercaptopurine	Oral	Induction and maintenance	Azathioprine: 2-2.5 g/kg Mercaptopurine: 1-1.5 g/kg	Azathioprine: 2-2.5 g/kg Mercaptopurine: 1-1.5 g/kg	Nausea, vomiting, hepatitism, bone marrow suppression, pancreatitis,	[22,23]
Anti-TNF	Infliximab Adalimumab Golimumab	IV Subcutaneous	Induction and maintenance	Infliximab: 5 mg/kg weeks 0, 2, and 6 Adalimumab: 160 mg week 0, 80 mg week 2	Infliximab: 5 mg/kg every 8 wAdalimumab: 40 mg every 2 wGolimumab: 100 mg every 4 w	Infusion/injection site reaction, infection,melanoma, reactivation of latent TB and hepatitis B,	[22,23]

	Golimumab: 200 mg week 0, 100 mg week 2

Drugs used in the management of ulcerative colitis

Ulcerative colitis relies on the extremity of the disease, its subtype, patient preference. Most frequently used drugs for its cure and management are an anti-inflammatory agent which mostly includes 5-aminosalicylates like olsalazine, mesalazine, and balsalazide, which can treat slightly to average attacks and can sustain remission in UC and immunosuppressive agents which includes azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus calcineurin inhibitors. Other categories of drugs include Corticosteroids, like prednisolone and anti–TNF-α-antibodies for ordinary to acute or serious conditions of IBD [21]. Table 2 shows the different drugs used in the treatment of ulcerative colitis.

Aminosalicylates

Sulfasalazine is the first-class drug of antibiotics. For the management of ulcerative colitis Oral 5-aminosalicylic acid (5-ASA) is taken.Mesalamine (5-ASA) is usually absorbed from the upper region of the intestine; particular delivery of drugs into the colon may be amoreacceptablemethod of drug delivery with fewerside effects and more potency. Due to side effects in those with sulfa allergy and nausea, newer forms of 5-ASAs were created specific for its activity on the GI tract. The mechanism of action of 5-Amino salicylates includes the stimulation of class of nuclear receptors, which mainly include cell proliferation and inflammation. It helps in decreasing the production of chemoattractant leukotriene and slows down the cellular release of interleukin-1 and 2[24]. Wang*et al.* (2016) have studied 5-ASA Common side effects like flatulence, nausea, abdominal pain,diarrhea, headache, dyspepsia, nasopharyngitis[25].Management of mesalamine usingacombination of rectal and oral provides complete relief of distal UC than rectal or oral therapy alone[26].

Corticosteroids

These drugs act via glucocorticoid receptor in the cell nucleus and immune response modulates but due to the steroidal nature of these drugs, they can improve corticoid resistanceandcorticoid dependency,which their maximum applicability in UC[27]. These drugs are used for mild to common conditions of UC. But in the acute type of IBD and for patients who do not show any effect to corticosteroids, Immunosuppressive drugs like azathioprine, 6-mercaptopurine, methotrexate, cyclosporine, tacrolimus, etc. are the next line of drugs and play an important part in the treatment IBD. But the safety profile of this treatment is still an issue [28].

Thiopurines

The thiopurines, 6-MP and AZA have been said to sustain remission in both CD and UC. AZA is the prodrug to 6-MP as it is metabolized to 6-MP. Both drugs are thiopurine analogs that work through 6-thioguanine nucleotide (6-TGN), which is the active metabolite, which in turn stops the synthesis of DNA and RNA and also the apoptosis of T-cell [29,30]. AZA/6MP inhibits purine synthesis and ultimately DNA and RNA synthesis. They also stop T-and B-lymphocyte multiplication. However, the precise mode of action at UC is not known.They can be used to cause and retain remission in UC with effectiveness rates of 60–70%. They can reduce the dose or stop steroids in patients who have better with steroids and chronic active disease not completely controlled with steroids[31].

Anti-tumor necrosis factor therapy

Infliximab is a chimeric monoclonal antibodythatis used against tumornecrosis factor-alpha(TNF-α) and also used in the management of autoimmune diseases.For patients with average-to-acute UC who are intolerant of mesalazine (5-ASA) products and immune modulators, infliximab is used for remission induction. UC patients failed mesalamine and immune modulators therapy, then Infliximabcan be used for management of remission in UC patients. The use of infliximab in ulcerative colitis patients whose therapy is based on steroids is unclear. Infliximab can be used in acute steroid-resistant in ulcerative colitis patients who are unwilling to undergo surgery. The cases of hepatosplenic lymphoma have been described in younger patients on infliximab who were on relatedimmune-suppressive agents [32,33].

Challenges in the maintenance and treatment of ulcerative colitis

Many drugs are available for the therapy of ulcerative colitisi.e. 5-aminosalicylic acid, oral or systemic corticosteroids, immune modulator, etc. but these drugs are associated with many serious side effects after long-term use or have a certain disadvantage or not suitable for the use in some patients. Reduction of drug-related side-effects is the main challenge of therapy in ulcerative colitisi.e. (weight loss, rectal bleeding, anemia, tachycardia, and bowel distension by drug delivery to the colonwhich is site-specific[34]. Kim*et al.* (2006) have studied to design a delivery system, which delivers the maximum amount of drug to the specific site at the right period timein the body that increases efficacy, compliance is a great [35]. There are numbers of agents taken for the therapy of ulcerative colitis diseases but they show adverse effects like diarrhoea, peptic ulcers,nephron and hepatotoxicity, vomiting, glaucoma, Cushing's syndrome,etc. [36-38]. To target the drugs,particularlyto the colonic part of GIT is the main challenge[39]. Synthetic drugs have variousdrawbacks and for this reason, safeandefficacious drug treatment for the UC is the problem. The damage to skeletal and growth development is because of the absence of balanced nutrition is another problem for children with IBD. To solve these difficulties, proper nutrition and appropriate anti-inflammatory therapy are the best options.

Role of microparticlesand nanocarrierin ulcerative colitis

Microparticles and Nanocarrier systems are used for the targeted type of drug delivery for the management of ulcerative colitis.Microparticles are suitable for a wide variety of drug delivery applications, and they offer many advantages.

- Their small particle size offers improved reproducibility in the drug release mechanism.
- They offer improved control over the release rate of the drug.
- A microparticle offers immediate, modified, delayed, pulsed, sustained, and extended-release.
- They allow the preparation of dosage forms for colon delivery through the use of coatings designed.
- Their reduced particle size gives them the potential to improve bioavailability.

The major motive of this delivery system is to target the high concentration of active ingredients to the site in the inflamed intestinal tissues to enhance the therapeutic efficacy and minimizing the side effects[40]. Micro and Nanoparticle systems providea selective drug targeting to the specific site with alossin the needed efficacious drug dose and side effects[41].So the formation of a novel site-specific drug delivery system that will increase the drug release inthe inflamed tissues without causing any harm to normal tissues and then decrease the side effects of the drug is needed.

The major step in this direction is preparing pharmaceutical dosage forms with reduced sizes, which will enhance the time of their residence in the colonic part. The most common characteristic of IBD is diarrhea that causes the streaming of the dosage form (rapid transit of large dosage forms). By decreasing the size of dosage forms (e. g. pellets) the enhancement in the retention timecan be done. Further,the decrease in size to micrometer range will help toreduce the streaming effect (and thereby increase the residence time)and also helps in enhancing the bio-distribution of drug molecule[42,43].Lately, many innovative ideas have been explored for the management of IBD. The main motive behind thedevelopment of these targeted drug delivery systems was to reachsite-specific transport of active moieties to the inflamed tissue. These drug carrier systems not only prevent degradation of activemoieties against various physiological changes happening during IBD but also increase the therapeutic effectiveness and lessen the incidence of systemic adverse drug reactions. Research and development in the treatment of IBD are observing steady-state

progress in terms of thedevelopment of upgraded and smart drug delivery systems, and highly effective therapeutic agents. One can say that the idea of attaining effective and site-specific targeting for the treatment of IBD will soon be able to knock the doors of reality.

Mechanism of uptake of nanocarriers/microcarriers

The mechanism of uptake of nanocarriers/microcarriersforsite-specific drug delivery is depending upon the full information of the mechanism of disease and drug. In some studies, it has been stated that for ulcerative colitistreatment, microparticles range should be 10–300 µm to target specifically to the inflamed region of the colon. Carrier selection is very important for a particular drug i.e. either hydrophilic or lipophilic and also depends on the disordered situations as well as on the physicochemical nature of thedrug.The optimal particle size should be between 4 to 15 µm for improved localization and increased theresidence time of the drug at the site of inflammation [44-46]. To attain high localization in Payer's patches, intestinal lymphoid tissue, and lamina propria, there is the need to overcome such barrier/layer. In the case of UC, as the disease severity increases, the protective mucus layer starts becoming thinner. This pathophysiology of the mucus layer increases the mucosal permeability and helps in the proper location at its inflamed sites. Size-dependenttranslocation of MP and NP across colonocytes in the healthy GI tract containsfig. 4Lamprecht*et al.*(2001) shows that the mechanism of nanocarriers in ulcerative colitis thatnanocarriers system systems to target the inflamed mucosa are a promising strategy in ulcerative colitis treatment[46].

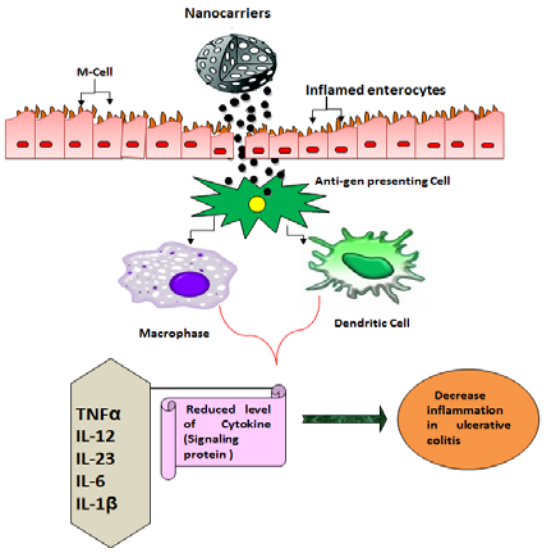

Fig.4: Show the mechanism of nanocarriers uptake in ulcerative colitis

Reducing the particle size of drug delivery systems is believed to increase colonic residence time but can also provide additional benefits for IBD therapy, such as a selective accumulation in inflamed tissues. Nanocarriersare taken up by an increased number of immune-related cells in active inflammation and to suppress inflammation via multiple pathways, like inhibiting the production of pro-inflammatory cytokines (i.e., TNF-a, IL-1b or IL-8). In some earlier studies, the different carriers system used in ulcerative colitis is shown in table 3.

Table 3:Different carrier system used in ulcerative colitis

Drug	System used	Inference	Reference
5-Aminosalicylic acid	Alginate blend microspheres	No Systemic toxicity was observed and great potential application in inflammatory bowel disease.	[48]
	Microparticles	Increase therapeutic efficiency, mucoadhesive and controlled release.	[49]
	Chitosan-ca-alginate microparticles	5-ASA loaded microparticles have the potential for intensive mucoadhesion and controlled colon-specific delivery	[50]
	N-succinyl-chitosan microparticles	Drug targeting, biocompatible, low toxicity.	[51]
Cyclosporine	Polymeric nanocarriers	Minimizing systemic exposure and associated adverse effect.	[52]
	Lipid nanoparticles	Enhancing efficacy and reducing the risk of nephrotoxicity and decrease renal damage.	[53]
	Eudragit S 100 solid nanomatrix	Improved nephrotoxicity and increase bioavailability.	[54]
Prednisolone	Conjugate microspheres	Eudragit-coated Ch-SP-MS were considered potentially suitable for *in vivo* or practical application as a specific delivery system of PD to IBD sites	[55]
	Silica microparticles	Increase bioavailability by sustaining the drug release and enhancing drug permeability.	[56]
	Microspheres	Reduce toxicity, Ch–SP-MS/Eul reduced significantly the thymicatrophy caused by PD.	[57]
Budesonide	Chitosan coated ca-alginates microparticles	Eudragit coating has successfully sustained the release of BDS in the upper GIT (pH 2.0 and 6.8) while providing the potential for efficient release of BDS in the colon (pH 7.4).	[58]
	Microparticles	Site-specific and controlled delivery and reduce toxicity.	[59]
Vancomycin	Chitosan-based micro and nanoparticles	Micro and nanoparticles improve the release in the colon	[60]
Glucocorticoster	Collagen microparticles	The drug was not influenced by the pH of the release medium. Binding to the	[61]

oids	particles did not affect the stability of hydrocortisone. Collagenmicroparticles can be successfully used as a carrier system for lipophilic steroids.

Role of probiotics in thetreatment of ulcerative colitis

Probiotics are 'live microorganisms which when given in sufficient quantity, are beneficial to the host.Probiotics are microorganisms that we take into our bodies to support our health. Commonly, they're strains of bacteria that can help improve our digestion.The health benefits of Probiotics are shown in fig. 5 [61]. Probiotics are that rare supplement from which almost everyone can benefit. Probiotics assist with a lot of health concerns, such as healthy digestion, healthy metabolism, and even increased weight loss. A poor diet, too much stress, and a lifetime of antibiotics have likely disposed of the majority of the good bacteria.The identification of the microbial environment and cytokine expression as key components of intestinal mucositis, probiotics represents a promising therapeutic option. When probiotics are administered in sufficient numbers, they can provide beneficial physiologic or therapeutic activities. Bacteria can be derived from various sources, such as cultured.food and normal human microbiota, but must certain criteria included complete identification at genus, species, and strain level;antimicrobial substances; safety for consumption; may apply probiotic properties is impressive. Some are listed in table 4. For nutrition,the strains categorized as lactic acid bacteria are of importance, and out of them, are of genera *Lactococcus* and *Bifidobacterium*.

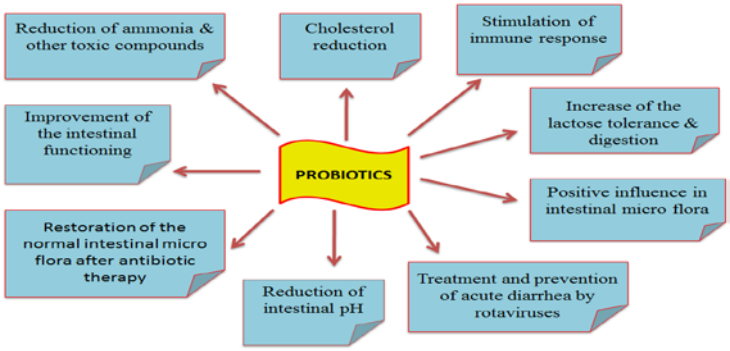

Fig.5: Health benefits of probiotic

Table 4: Microorganisms commonly used as probiotics

Lactobacilli	Bifidobacteria	Others	References
L. CaseiShirota	*B. longum*	*Escherichia coli Nissle*	
L. rhamnosus GG	*B. bifidum*	*Saccharomyces boulardii*	[62]
L. johnsonii	*B. infanitis*	*Enterococcus faecalis*	
L. acidophilus	*B. lactis*	*Lactococcuslactis*	
L. gasseri	*B. breve*	*Propionibacteria*	
L. reuteri	*B. animalis*		
L. casei	*B. adolescentis*		
L. fermentum			
L. crispatus			

Lactobacilli are Gram-positive, non-spore-forming, and non-flagellated rods or coco bacilli, aerotolerant, fastidious, acid-tolerant, and strictly fermentative[63].The different probiotic strain has adifferent ability, even within the same species, it is different. Different strains of the same species are always distinct and may have different areas of attachment (site-specific), specific immunological effects, and activity on a healthy vs. an inflamed mucosal milieu may be different from each other.The research on probiotic today aims at the characterization of microbiota in each individual, analyzing the species constitution as well as the numberofdifferent bacteria in the intestine. The objective is to learn to comprehend host-microbe interactions inside the gut, microbe-microbe interactions inside the microbiota, and the joint healtheffects of these interactions. The aim is to study the microbiota in the nutritional management of gut-related problems and as an origin of new microbes for future probiotic bacteriatherapyapplications. This will finally include organisms notably isolated to provide site-specific actions in disorders like IBD[64].

Probiotics alter the function of the mucosal immune system making it more anti-inflammatory and less pro-inflammatory;especially, probiotics can inspiredendritic cells to make them less responsive and less reactive to bacteria within the lumen. Probiotics increase the production of mucus and the patient will finally have a thicker layer, which saves the invasive bacterias. Probiotics supplements may lower the side effect of individual drugs. DifferentProtective actions of probiotics show in table 5.

Table 5:Protective action of probiotics

Microflora	Action of microflora	Reference
Bifidobacteria species	Reduced incidence of neonatal necrotizing enterocolitis Balancing intestinal microflora, treatment of viral diarrhoea	[66]
Lactobacillus strains	Improved mucosal immune function, mucin secretion, and prevention of disease. Lactose digestion improved decreased diarrhoea and symptoms of intolerance in lactose intolerant individuals, children with diarrhea, and in individuals with short–bowel syndrome.	[67]
LactobacillusAcidophilus	Significant decrease of diarrhoea in patients receiving pelvic irradiation.	[68,69]
Lactobacillus Plantarum	Lowered serum cholesterol levels.Reduced incidence of diarrhoea in daycare centers when administered to only half of the children.Especially effective in reducing inflammation in inflammatory bowel; enterocolitis in rats, small bowel bacterial overgrowth in children, pouchitis.Reduced pain and constipation of irritable bowel syndrome.	[70-72]
Lactobacillus rhamnosus	Enhanced cellular immunity in healthy adults incontrolled trials.	[73]

Escherichia coli Nissle 1917 (EcN)	Anti-inflammatory effect and prevent relapse.	[74,75]
Streptococcus	The Strain of *Streptococcus thermophilus*has also reduced the risks of AAD (antibiotics-associated diarrhea).	[76]

Probiotics and ulcerative colitis

Escherichia coli Nissle 1917 and *Saccharomyces boulardii*were used as probiotics. Probiotics have living microorganisms that providehealth benefitsto the host.*EscherichiacoliNissle* 1917 established therapy with mesalazine in patients with ulcerativecolitis.It was seen that the probiotic drug *E. coliNissle* 1917 showstheeffectiveness and was declared to be safe to maintain remission and was equal to mesalazine in patients with ulcerative colitis. The efficacy of probiotic therapy further tells about thepathogenetic importance of the enteric flora [76].

Fábrega*et al.* (2017) have shown theIntestinal Anti-inflammatory Effects from *Escherichia coli Nissle* 1917 in DSS-Experimental Colitis was studied in Mice. Oral administration of purified EcN OMVs (5µg/day) significantly reduced DSS -induced weight loss and ameliorated clinical symptoms and histological scores. This study showed that EcN OMVs can mediate the anti-inflammatory and barrier protection effects previously reported for this probiotic in experimental colitis[77].

Naidoo*et al.(*2011) Studies have shown the significance of intestinal bacterial flora in the pathogenesis of inflammatory bowel disease. It has therefore proposed thataltering the bacterial flor a with probiotics will reduce the inflammatory process and stop the relapses in ulcerative colitis (UC)[78].

Pronio*et al.*(2008)studies that show that the period, VSL#3-treated patients showed a notable loss in PDAI score and a major enhancement in the percentage of mucosal CD4CD25high and CD4 LAP-positive cells compared with baseline values.Different samples were taken at different points a significant reduction in IL-1 mRNA expression was seen, and a major enhancement in Foxp3 mRNA expression[79].

Zocco*et al.*(2006) ware studied aminosalicylates are the mainstay of therapy to prevent relapse of quiescent ulcerative colitis. The rationale for using probiotics is based on the evidence implicating intestinal bacteria in the pathogenesis of this disorder. *Lactobacillus GG*looks to be effective and safe for maintaining remission in patients with ulcerative colitis, and it could represent a good therapeutic option for preventing relapse in this group of patients[80].

Loren *et al.*(2017) investigated the therapeutic benefits of *Lactobacillus Plantarum* (CECT7484, CECT7485) and *PediococcusAcidilactici* (CECT7483)) in a murine model of colitis. Result suggests that the selected probiotic group significantly reduces colitis severity compared to untreated controls [81]Wang*et al.*(2015) has studied the main mechanisms have not been completelyexplained; the antioxidant activity of probiotics seems to play an important role in reducing inflammation. Several studies have reported that probiotics particularly *Lactobacillus* species, exhibit strong antioxidant activity[82]. Chauhan*et al.*(2010) have recently, *Lactobacillusfermentum* has been studied for use as a supplement in the management of inflammatory bowel disease (IBD). Reinforcing the effects of *L. Fermentum* in inflammation, Chauhan and coworkers assessed its antioxidative efficacy in a colitis mouse model. Results proposed that the selected strain of *Lactobacillus* exhibits significant antioxidant activity. Also besides, probiotics seem to upregulate the level of antioxidant enzymes [83].

CONCLUSION

The current therapeutic goals are to achieve clinical remission along with mucosal healing, avoidance of complications such as side effects of the drug and to improve the quality of life. The use of probiotics to increase the health of the intestine and used to block or manage intestinal disorders. They may prevent the induction of inflammatory reactions. Probiotics must be inspected for efficacy in the prevention and management of a wide spectrum of gastrointestinal diseases, like antibiotic-associated diarrhea. There are many benefits to probiotics over conventional therapy, including various things like low cost, the fact that probiotics are improbable to enhance the incidence of antibiotic resistance, and the multiple methods by which probiotics stop pathogens, therefore limiting the chances for the development of resistance against the probiotic. At present, no microencapsulated probiotic cells exist in the market. Thus, the search is increasing on new delivery strategies that can provide therapeutic benefits to colitis suffered patients. It has been concluded from the above study that micro and nanoparticulate carrier and probiotics system appears to be the most promising approach by specifically accumulating in the inflamed intestinal region.

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All the authors have contributed equally.

CONFLICTS OF INTERESTS

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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