Review

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Role of inulin as prebiotics on inflammatory bowel disease

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Summary **The present review is focused on the prebiotic impact of inulin on the management of the gastrointestinal disorder. Prebiotics can be described as "non-digestible food ingredient stimulating the growth of a certain number of bacteria in the colon, which can improve the host health". In 2004 this definition was modernized to include other areas that may benefit from selective targeting of particular microorganisms: "selectively fermented ingredients that alter the configuration and activity in the gastrointestinal microbiota that confer positive effect". The positive impact of prebiotics in experimental colitis and human inflammatory bowel disease (IBD) has already been established. Prebiotics shows a positive effect in the prevention of IBD by modulating the trophic functions of the flora. Inulin enhances the growth of indigenous *lactobacilli* and/or *bifidobacteria* by inducing colonic production of short chain fatty acids (SCFA's) and these properties are related to decreased mucosal lesion scores and diminished mucosal inflammation. Inulin shows a positive approach to retain microbial populations and to support epithelial barrier function by their prebiotic effect which helps in the host defense against invasion and pathogens translocation (endogenous and/or exogenous) and in the inhibition of gastrointestinal diseases and this impact should be verified in further clinical studies. In the present review, we discussed the positive effect of prebiotics in rat IBD models and in human subjects along with their potential protective mechanisms. Preclinical and clinical data revealed that the gut mucosal barrier would be improved by the use of prebiotics in IBD.**

Keywords: Inulin, prebiotics, microflora, inflammatory bowel disease

1. Introduction

Inflammatory bowel disease (IBD) refers to a variety of multifactorial dysfunctions that arise in the digestive system (*1*) and are recognised by intense inflammation of the gastrointestinal tract (*2*) due to abnormal immune responses (*3*). This gastrointestinal inflammation includes Crohn's disease (CD) and ulcerative colitis (UC). Recent findings revealed that IBD complication is originated from genetic, ecological and unusual immunological factors (*4*). The eating regimen, lifestyle and other vulnerable endogenous elements such as gut microflora are involved in the development of disease (*2*). The research studies proposed that the human bowel microbiota generates antigenic factors which trigger the persistent inflammation of the intestinal mucosa as observed in CD and UC (*5-7*). This information has directed to an emerging therapeutic tactic that pins the microbiota of patients having IBD using agents like prebiotics (inulin) which work primarily by stimulating the growth or increasing the numbers of certain bacteria and thus quantitatively transforming the microflora (*8*). When prebiotics reaches to the colon are fermented by anaerobic bacteria, yielding short-chain fatty acids (SCFA). As a result, intraluminal pH decline (*9*). An increase of *Bifidobacteria*, *Lactobacilli* and non-pathogenic *E. coli* in colon are accountable for antimicrobial activity, immunomodulation, and induction of an immune response, and improvement of barrier activity that confers health benefits to the host (*10-12*).

The management of IBD consists of employing antibiotics, immunomodulators, and biological therapies (Table 1), even though they show toxicity have less therapeutic benefits for the treatment of UC (*13*). In addition, the present treatments are frequently directed against the highly intense adaptive immune response of the host but fail to precise probable environmental

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Table 1. Outline of the approaches used for IBD (*18*)

Therapeutic Agent	Disease Conditions	Method of Delivery
5-Aminosalicylate	Mild to moderate	Oral, topical
Corticosteroids	Mild to critical	Oral, topical, Intravenous
Immunomodulators: - Azathiopurines - 6 Mercaptopurines - Cyclosporin A - TAcrolimus - Methotrexateen	Moderate to critical steroid-dependent and steroid-refractory disease fistulising	Oral, topical, injection
Antibiotics: - Metronidazole - Ciprofloxacin	Active	Oral, intravenous
Biological Therapies: - Adalimunab - Certolizumabpegol - Inflixmab	Modern tocritical Fistulising	Intravenous, injection, infusion
Probiotics & Prebiotics: - EscherichiacoliNissle1917 - Fructooligosaccharide - Glucomannanhydrolysate	Remission maintenance	Ingestion

Table 2. Research studies that recommend intestinal microflora involvement in pathological process of IBD

Subjects retained under precise germ-free conditions do not experienceinflammation unless microorganismis introduced (*19,20*)
In patients with CD, the number of adherent mucosal bacteria is increased (*21*)
Inflammation arises in intestinal regionswith the maximum number of bacteria (*22*)
Luminal and mucosa-linked microflora of IBD subjects varies from healthy subjects (*23,25*)
Alteration of the fecal stream triggers clinical progress in Crohn's patients (*25*)

triggers like intestinal microbiota that provokes and perpetuate these ailments (Table 2). In addition, a microbial imbalance exists between disease-causing and defensive intestinal microflora in subjects with IBD (Table 3).

The above drawback led to newer approaches for the treatment of IBD-like prebiotics, probiotics or a combination of the two (synbiotics). Using prebiotics as a therapeutic agent or adjuvant to conventional therapy could prove an efficacious tool for the treatment of a series of physiological disorders. The data obtained from limited preclinical and clinical findings have studied the impact of prebiotics on UC and CD (*14-16*). The various research findings show that unrefined fibre-rich carbohydrates show a prominent effect on the management of CD (*17*).

Table 3. Microbial imbalance among disease-causing and defensive intestinal bacteria in subjects with IBD (*26*)

Defensive Bacteria	Disease-causing Bacteria
Bifidobacterium	*Selected Bacteroides*
Lactobacillus	*Enterococcus faecalis*
Streptococcus salivarius	*Enterobacter cloacae*
Saccharomyces boulardii	*Fusobacterium*
Clostridium butyricum	*Intestinal Helicobacter*
E. coli Nissle 1917	*Entero-invasive E.coli*
Ruminococci	*Eubacterium*
	Peptostreptococcus

2. Inulin a versatile biopolymer

2.1. *Origin and identity*

Rose, a German scientist discovered inulin in 1804 from the roots of *Inulahelenium*, a genus of perennial herbs of the group Compositae, inhabitants of the temperate regions of Europe, Asia, and Africa (*27*). Inulin was also referred by other names such ashelenin, alantin, meniantin, dahlin, sinantemin, and sinisterin.

Inulin comes under a general class of fructose-containing polymers known as fructans. Fructans assist as storage polymers in numerous members of the Compositae family such as *Cichoriumintybus* (chicory), *Inulahelenium* (elecampane), *Taraxacumofficinalis* (dandelion) and *Helianthus tuberosus* (Jerusalem artichoke). Inulin is extracted from chicory is a natural polydisperse carbohydrate (*28*). Inulin is a fructan which mainly comprises of 1, 2-[3-1inked d-fructofuranose units bound by an (od-132) type linkage to a terminal glucose moiety. By assessment, inulin primarily made up of linear fructose units tied by a β-(2-6) glycosidic bond (Figure 1) (*31*).

2.2. *Versatile applications*

Inulin a versatile biopolymer has a variety of applications in the Pharmaceutical arena, Food arena

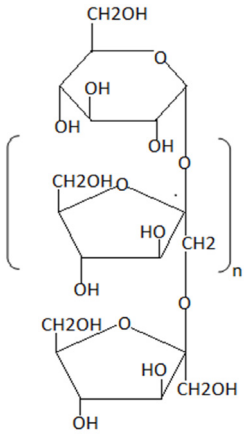

Figure 1. The molecular structure of inulin.

Table 4. Key Applications of Inulin in a distinct area

Category	Application/Uses	*Ref.*
Pharmaceutical Applications	*Stabilisation*	
	- Anhydrobiosis	(*29*)
	- Protein stabilization	(*30*)
	Drug Delivery	
	- Solution behaviour alteration	
	• Solution rate enhancement	(*31*)
	- Local drug delivery	
	• Colon targeting	(*32*)
	• Pulmonary delivery	(*33*)
	Physiological and disease modifying effect	
	- Systemic	
	• Vaccine Adjuvant	(*34*)
	• Diagnosis of kidney functioning	(*35*)
	- Gastrointestinal tract	
	• Constipation	(*36*)
	• IBD & colon cancer	(*37*)
Food Applications	*Fibre enrichment*	(*38*)
	As a prebiotic	(*39*)
	As a fat replacer	(*40*)
	As a sugar replacer	(*41*)
Nutritional and health benefits	Function as dietary fiber	(*42*)
	Effect on lipid metabolism	(*43*)
	Effect on constipation and stool frequency	(*44*)
	Bifidogenic effect	(*45*)
	Reduction in risk of gastrointestinal diseases	(*46*)
	Stimulation of the immune system	(*47*)
	Intestinal acceptability	(*48*)

and also have nutritional and health benefits. In the present review, diverse application of inulin has been summarized in Table 4, but the study mainly focused on the prebiotic impact of inulin on IBD.

Prebiotics can be described as "non-digestible food ingredient stimulating the growth of a certain number of bacteria in the colon, which can improve the host health" (*53*). In 2004 the definition of prebiotic was modernized to involve other areas that may take advantages from selective targeting of specific microflora: "selectively fermented ingredients that alter the configuration and activity in the gastrointestinal microbiota that confer positive effect" (*49*). Indigenous *Bifidobacteria* and *Lactobacilli* microbial genera are

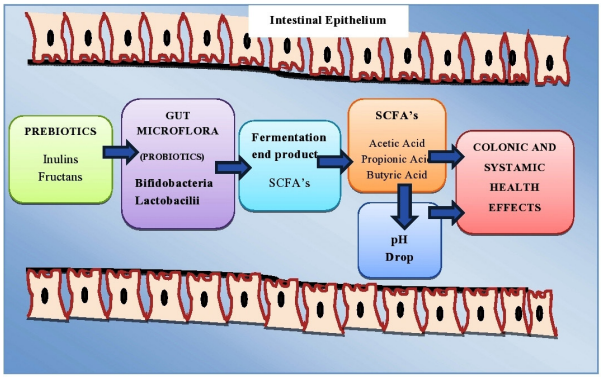

Figure 2. Mechanism of prebiotic action.

directed for selective stimulation (*50*).

Prebiotics aid as a source of food for probiotics to raise, proliferate and increase in numbers on the bowel microflora. Through the fermentation by the anaerobic microflora, short-chain fatty acids (acetate, propionate, and butyrate) are formed as the end products which are responsible for colonic pH drop and prevent the development of pathogenic microflora (Figure 2). These positive effects are mainly based on the nature and amounts of the prebiotic used in an eating regimen, as well as the density of *Bifidobacteria* on the gut of the host (*51,52*). Moreover, these prebiotics shows a positive effect on the deterrence of IBD by modulating the trophic functions of the flora and providing other health benefits.

3. Involvement of intestinal flora in IBD

Improvement in the last few years has been done to acquire a better consideration but still, the precise pathological process of IBD is quite unknown. Current finding in the etiology of IBD proposed that the combination of genetical, immunological and ecological parameters is responsible for the occurrence of this disorder. The role of intestinal microflora in the pathogenesis of IBD is well known (*53*), primarily in Crohn's condition. This persistent bowel inflammation usually appears at terminal ileum and colon, the zone with the maximum intestinal microflora concentration. Antibiotics and faecal diversion are the remedies for CD although regenerating endurance of the bypassed distal colon or intestinal matters infusion into the omitted ileum may cause a return of disease (*5*). In numerous rat models of chronic intestinal inflammation, the consequence of bowel microflora in the commencement and perpetuation of chronic bowel infection is most credibly validated (*54*).

After 56 days of birth transgenic rats HLA-B27 develop colitis in the presence of usual bowel microflora (*55*), while in non-transgenic rats, antibiotic-cured transgenic rats, and microbe-free transgenic rats there is no evidence of the occurrence of disease (*56,57*). Aggravation of colitis can be associated with an

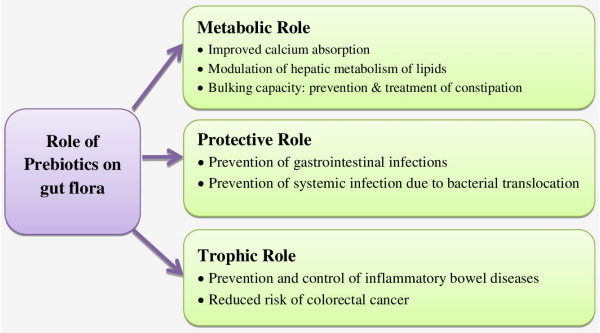

Figure 3. Role of prebiotics on gut flora.

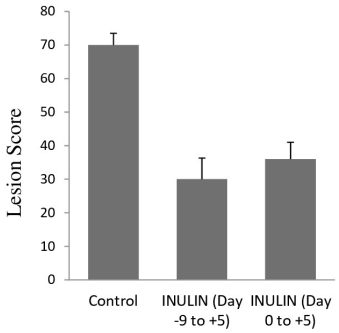

Figure 4. Histological scores in rats with colitis provoked by dextran sodium sulfate (DSS). Insulin-treated rats (400 mg/d) indicated lower lesion scores than controls (*$p < 0.05$ *vs*. control). Inulin treatment in progress either 9 days before exposure to DSS (day – 9 to + 5) or at the same time as the exposure to DSS (day 0 to + 5) and was continued for the 5 days on DSS (*75*)

amplified concentration of luminal Bacteroides species (*58*). In the distal intestine *Bacteroides* spp. is the most dominant. After surgical resection postoperative relapse of CD is related to amplify *Bacteroides* species (*59*). Most importantly, after monoassociation for 4 weeks *B. vulgate* causes intestinal inflammation in transgenic rats, while monoassociation with *E. coli* does not show any disease condition (*60*). As a result, all bacteria are not equivalent in their capability to cause intestinal inflammation.

4. Prebiotics in inflammatory bowel diseases

Numerous studies have verified the role of prebiotics on gut flora (Figure 3) and also verified that the metabolic functionality of the intestinal flora can be increased by utilization of prebiotics. For example, there is abundant proof revealing in human research that absorption of calcium improves by inulin-type fructans. Similarly, animal experiments have confirmed that the hepatic metabolism of lipids enhances by fermentation of oligofructose and may elude dysfunctions linked with non-alcoholic steatohepatitis and metabolic syndrome. The bulking capacity of inulin-type fructans shows benefits for metabolic bowel functions and can also help in the inhibition and treatment of constipation. The improvement in the gut barrier has also been shown by prebiotics treatment. Prebiotics are considered to be safe, non-toxic and shows a positive effect in the inhibition and management of gastrointestinal disease on the basis of large number studies on clinical trials (*61-70*).

4.1. *Inulin effect in animal models*

The prebiotics impacts on bowel inflammation already been studied in various animal models. Mice lacking *IL-10* gene impulsively develop colitis. There is a low level of *Lactobacillus* species in the colon in the neonatal period of these mice and also have an elevation in adherent and translocated bacteria (*71*). The count of lactobacilli in faeces was shown to normalize by rectal delivery of *Lactobacillus* reuteri and this prevents the expansion of colitis. In the same animal model, mucosal lesion scores and inflammatory activity is reduced by oral administration of either *Lactobacillus salivarius* or *Bifidobacterium infantis* (*72*). A genetically engineered bacterium in IL-10 knockout mouse model produces the anti-inflammatory cytokine IL-10 that prevent the onset of colitis (*73*). Though, the colitis provokes with the help of trinitrobenzene sulphonic acid in the rat did not diminish probiotic therapy with *Lactobacillus* plantarum (*74*). The experimental findings with probiotics have revealed that the impulsively grow inflammatory mucosal lesions in mice knockout of the *IL-10* gene is prevented by increasing the amounts of lactobacilli or bifidobacteria in the colonic lumen.

The inulin prebiotic impact was studied in dextran sodium sulfate (DSS) evoked distal colitis in a rat model, which histologically bears a resemblance to human UC (*75*). By daily administration of inulin through oral route the indigenous lactobacilli counts are amplified in the lumen of the caecum and also decrease the pH of colonic. Inulin nourishing prolonged the saccharolytic section (only right colon) that brings about an acidic atmosphere in the left colon. In the rats with DSS evoked colitis themucosal inflammation and histological damage scores are reduced by orally administered inulin (Figure 4) (*75*). Moreover, the rats fed with inulin exhibited a lower degree of mucosal damage and reduced harshness of crypt damage, as compared to controls. Management with orally administered inulin had been equally showing positive effect whether treatment offered ahead of or during exposure of DSS.

For the management of chronic colitis making use of prebiotics are promising and also have been executed frequently in animal models (Table 5). Nourishing inulin and oligofructose combination at 5 g/kg body weight diminishes intestinal inflammation in transgenic rats (*76*). The model HLA-B27 transgenic rat is used to judge prebiotic action working mechanisms in chronic colitis in this research study. This positive outcome was seen with a rise of intestinal bifidobacteria and

Table 5. Prebiotic treatment on a colitis induced animal model

Ref.	Treatment	Animal Model	Result
Videla *et al*. (*76*)	Dietary inulin	DSS-induced colitis in rats	Improvement distal colitis
Holma *et al*. (*82*)	Galacto-oligosaccharides	TNBS-induced colitis in rats	No reduction of colitis
Moreau *et al*. (*81*)	Oligofructose	DSS-induced colitis in rats	No reduction of colitis
Hoentjen *et al*. (*77*)	Oligofructose-enriched inulin	HLA-B27 transgenic rat	Reduction of colitis
Daddaoua *et al*. (*80*)	Goat milk oligosaccharides	Hapten-induced colitis	Colitis reduction
Lara-Villoslada *et al*. (*79*)	Goat milk oligosaccharides	DSS-induced colitis in rats	Colitis reduction

Table 6. Clinical trials of prebiotic treatment in IBD

Ref.	Study	*n*	Clinical Condition	Treatment	Duration of Treatment	Result
Welters *et al*. (*83*)	Double-blind placebo-controlled trial	20	Chronic pouchitis	Dietary inulin 24 g/d	6 week	Effective in the treatment of chronic pouchitis
Lindsay *et al*. (*85*)	Open-labeled trial	10	Active CD	Synergy 15 g/d	3 week	Reduction of disease activity

lactobacilli. Similarly, colitis-prone rats nourish by prebiotic combination (inulin and oligofructose) decreases mucosal proinflammatory cytokines and also immunoregulatory altering growth factor-β is amplified. The research studies reported a positive effect in transgenic rats with inulin plus probiotics (*77*). Diminished clinical indications and amplified MUC-3 manifestation were perceived compared with control rats in dextran sodium sulphate evoked colitis rats which were nourished with goat's milk oligosaccharides (*78*). In trinitrobenzene sulfonates provoke colitis rats, the colonic inflammation and necrotic lesions are also reduced by goat's milk oligosaccharides as compared with control rats (*79*). Though, it is not necessary that all findings using prebiotics shows a positive effect. Moreau *et al*. (*80*) reported oligofructose to be worthless in fixing dextran sodium sulfate evoked intestinal inflammation in rats, and Holma *et al*. (*81*) found same inefficaciousness of galacto-oligosaccharides in trinitrobenzene sulfonate induced-intestinal inflammation in rats.

4.2. *Inulin effect in human subjects*

Though there exists a scarcity of human studies utilizing prebiotics, a number of the emerging finding indicate that there is a prospect of this therapy modality. After colectomy for ulcerative colitis inulin shows a positive effect in the management of chronic pouchitis (*82*) Furrie *et al*. observe the usage of synbiotics (prebiotics plus probiotics) in 18 subjects with functional UC with the help of anew randomized, double-blinded controlled trial (*83*). This treatment involved grouping of prebiotics inulin and oligofructose. In the synbiotic nourished group, sigmoidoscopy inflammation scores were diminished as matched with the placebo group. The levels of intestinal TNF and IL-1a were also diminished. Moreover, the rectal culture revealed more epithelial regeneration and reduced inflammation in the synbiotic-treated subjects. A tiny, open-labeled trial of 10 active CD subjects, 21 days of 15 g oligofructose and inulin oral administration shows a substantial lowering of the illness condition (*84*) (Table 6).

4.3. *Inulin beneficial effects in other medical conditions*

Inulin also shows a positive impact in the number of gastrointestinal complication, like management of infectious colitis, toddler diarrhoea, improvement of lipid metabolism minimised the risk of chemically induced colon cancer, improved absorption of calcium, relief of constipation, and management of diet intolerance (*85-92*).

5. Conclusion

Inulin is a promising nutraceutical in numerous medical conditions, including IBD. It is convenient to intake, economical, and has no major toxic impacts and may develop into an interesting adjunct to standard salutary in IBD. The dietetic use of inulin proposes a potential tactic to maintain health and wellbeing and to manage the progression of disorders. In human IBD, an inflated immune influence against commensal bacteria has been validated. Bacteria locally affect cytokine signalling, mucosal intrinsic responses and mucosal inflammation can also be down-regulated by certain bacteria. Saccharolysis by inulin in the large intestine support the growth of bifidobacteria and lactobacilli. Due to these impacts, there is a reduction in mucosal inflammation of IBD as illustrated in experimental models. Bacteria producing lactic acid can prevent endogenous microorganism from reproducing and obstruct adhesion and incursion of microorganism from outside the body. In this way, the prebiotic impact of inulin shows a positive effect on the barrier function of the bowel. In this manner, the prebiotic approach is a beneficial adjunct for susceptible subjects such as patients with severe disease and subject with persistent gastrointestinal disorders, such as colonic cancer and gut inflammation. In preliminary clinical trials, promising results have been achieved, but more studies

are required to ensure the therapeutic use of inulin for the effective management of IBD.

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