SHORT COMMUNICATION

Probiotics and Herbals as a Boom in 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. In its most limited form, it may be restricted to the distal rectum, while in its most extended form, the entire colon is involved. UC is identified by mucus diarrhea, tenesmus, bowel distension, and anemia. 5-aminosalicylic acid drugs, steroids, and immunosuppressant are used for therapy of UC. The annual occurrence of disease in Asia, America, and Europe was estimated to be 6.3, 19.2, and 24.3/100,000 people years. The main challenges in the management of the disease are drug-related side effects and local targeting. To overcome these challenges, probiotics overcome drug-related adverse side effects and local targeting. On ingestion, the probiotics can result in health beneficial effects. Probiotics are mainly used as gut modulators but are also nowadays explored for their use in UC.

Key words: 5-amino salicylic acid, Crohn's disease, cytokines, *Mycobacterium avium*, probiotics, ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease are chronic inflammatory disease leads to alteration of the bowel wall.[1] UC is characterized [Table 1] by abdominal pain, inflammation at colon region, bloody stool, discomfort feel and apart from this, various extra intestinal manifestations are available (Pyoderma gangrenosum, erythema nodosum, primary sclerosing cholangitis, immune mediated disease rheumatoid arthritis, asthma, and psoriasis) which are related with inflammatory bowel diseases (IBD),[2] assuredly there is a high degree risk of neoplasia associated with colitis. Especially in patient suffered from colonic Crohn's disease and ulcerative panocolitis, as the UC formed in large intestine and last part of rectum, but in Crohn's disease it is distinguished by inflammation at any region of gastrointestinal tract (GIT) as per the reviewers suggestion UC and Crohn's disease have almost same pathophysiology and genetic pathway by which they are causing illness.[3] When we talk about GIT problem, irritable bowel syndrome is also a frequent issue. It is described by abdominal pain or discomfort during the passage of gas and defecation, associated with a change in consistency and frequency of stool.[4]

INTESTINAL MICROBIOTA: AN IMPORTANT CORE

Gut flora another name of intestinal microbiota is the name given today to the microbe population living in our intestine. Gut flora consists of ten to trillions of microorganisms having more than 500 types of bacterial species.[5] Interaction between the host and gut microbiota results in the variation of intestinal and systemic immunity against pathogens, secretion, sensation, intestinal motility, xenobiotics, growth, and development.[6] Apart from this, microbiota have effect on the host, which are further responsible for immunological, gene expression, psychological, and psychological

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functions.[7] Some evidence has been reviewed, to find the role of microbiota in normal gut function. Clostridium difficile can cause permitting colonization with antibiotics, which disrupt the intestinal microflora, ultimately lead to diarrhea or even colitis.[8] The disruption of intestinal microbiota results in infection in the colonic region. As per the data, gut microbiota play a key role to maintain the normal GIT function, disturbance with microbiota leads to the number of diseases.[6]

PATHOPHYSIOLOGY OF UC

The exact pathophysiology of UC is still unknown. As per the recent findings, [Figure 1] pathogenesis of UC remains unknown, in current years a number of findings conclusion point to an over incentive or insufficient regulation of the mucosal immune system as a crucial pathophysiological pathway, and then particular emphasis can be given to the analyses of immunologic reactions or mucosal inflammation. Many factors could affect the ulcerative colitis which could ultimately bring some immunological disorders. Apart from that, the effected person could be susceptible for infection cause by Commensal intestinal microorganisms. The first main cause is the deregulation of the immune system, which controlled immune responses to the usual microflora. In maximum (i.e., 95%) cases, deregulations of the immune system expend direct from the rectum in a continuous pattern involving part or every part of the colon.[9] A second cause is the epithelial cell abnormalities and alters in the content of gut microflora that facilitates an unusual mucosal immune response. A third cause is reduced gene expression, i.e., alteration of the gene that is CARD15/NOD2. UC is a chronic condition that contains large intestine and colon, where the entire organ or a portion of gastrointestinal is affected by inflammation. UC is the IBD which continual inflammation and ulceration which expend from rectum toward the caecum and is normally related with extra interleukin (IL-13) producing where, Crohn's disease is related to abundant production of IL-12/IL-23 and interferon-γ (IFN-γ)/IL-17, it usually involves part of ileum and colon where discontinuous ulceration and inflammation including granulomas occurs.[10]

Table 1: Basic symptoms of ulcerative colitis

S. no.	Initial symptoms of ulcerative colitis
1.	Nausea and vomiting lead to diarrhea
2.	Blood in stool
3.	Pain
4.	Arthralgia
5.	Fever
6.	Weight loss due to loss of appetite

SIGN AND SYMPTOMS

The main symptoms of UC are: diarrhea, abdominal pain, rectal pain, bloody stool, fever, weight loss, and malnutrition. In proctitis colitis, swelling of rectum lining and continuous sensation at the rectum site is majorly seen. In extensive colitis cramps, massive bleeding, and dilation of the colon are major symptoms and depend on the area and severity of disease.[11]

CONVENTIONAL TREATMENT STRATEGIES OF UC

Depending on the severity of disease accordingly, drugs are chosen, preferably anti-inflammatory drugs from 5-amino

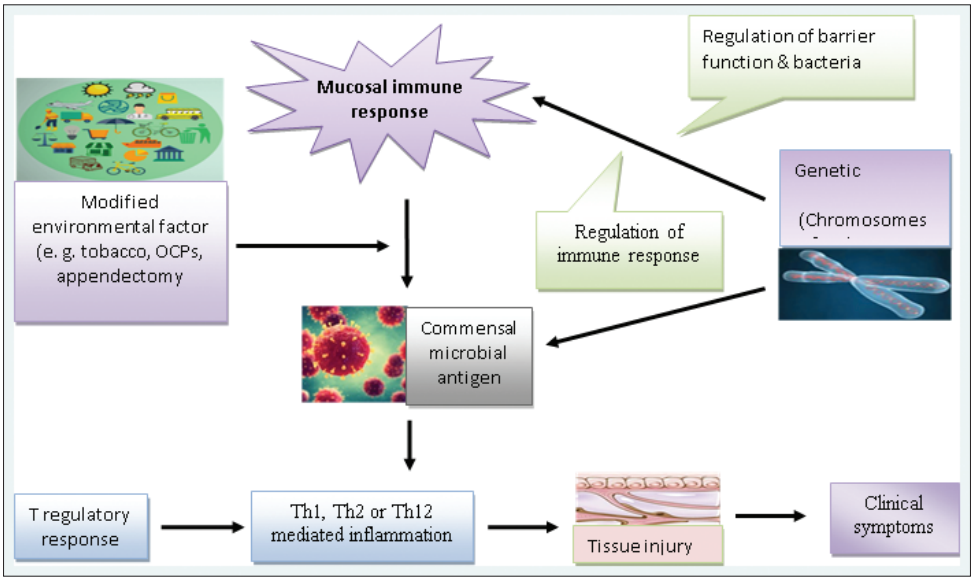

Figure 1: The basic steps which are responsible for the formation of ulcerative colitis

salicylic acid (5-ASA) class are used, i.e., mesalamine, sulfasalazine, balsalazide, and from the corticosteroid class commonly prednisone, methylprednisolone, and budesonide are given orally and rectally.[12] Prednisone and methylprednisolone suppress the immune system non-specifically, which is used to treat moderate to severe UC. Antibiotics are used at the initial stage of UC, but not in severe conditions. Mostly ciprofloxacin, metronidazole, and vancomycin are used.[13] The next class of drug is immunomodulators, when 5-ASA and corticosteroid class of drugs are unable to show effect against UC, at that stage immunomodulators play a key role by modifying the immune response, it may take several months to work, and drugs for this class are: methotrexate and azathioprine. In another category of drug, including inhibitors of tumor necrosis factor-α (TNF-α), i.e., infliximab and adalimumab,[14] it inhibits the production of TNF-α. One more class of drugs is added recently, new immunomodulators which includes thalidomide, tacrolimus, and mycophenolate mofetil. Some herbal drugs which are effective against UC are butyrate, liquorice, slippery elm, tormentil, *Boswellia serrata*, and bovine colostrum.[15]

5-ASA

This class of drugs has anti-inflammatory action. After oral ingestion of sulfasalazine, it is initially absorbed in the jejunum, inhibits the prostaglandins which are responsible for inflammation, it is systematically absorbed after cleavage from the 5-ASA. This class of drugs has anti-inflammatory action; by inhibition of IL-1, IL-2, and nuclear factor-kappa beta (NF-Kβ), it retard the function of monocytes. As per the recent findings, sulfasalazine inhibits the sulfide production. *In vitro* study shows patients who are taking 5-ASA, the fecal content has more sulfide than the normal fecal. Side effects include headache, vomiting, rashes, and male fertility. Sulfasalazine interacts with the absorption of folic acid, hence supplement enriched with folic acid should be used during the use of sulfasalazine.[16,17]

Corticosteroid

Basically, they are made up of steroid moiety, generally suppress the immune system by various pathways, by inhibition of IL-1, IL-2, IL-3, IL-4, IL-5, IL-IL-8, IFN-α, and arachidonic acid. In distal proctocolitis, topical steroid is administered with the help of suppositories or enema. Side effects include mood swings, weight gain, fluid retention, cataract, myopathy, osteoporosis, and weak immune system.[18,19]

Antibiotics

These are effective only at the occurrence of UC but not in the chronic stage. Drugs included in this class are: Metronidazole, ciprofloxacin, vancomycin, and tobramycin. Virulent *Escherichia coli* strains, *Mycobacterium avium,* and *Bacteroides* spp. are linked with the pathogenesis of UC. Antibiotics decrease the concentration of bacteria by changing the composition of gut microbiota.[20,21]

Immunomodulator

It is a new class of drugs which is used in the treatment of UC. It includes 6-mercaptopurine and azathioprine. It inhibits the proliferation of ribonucleotide and lymphocytes by suppression of T-cell and natural killer. These drugs also show anti-inflammatory action where the side effects of this class of drugs include diarrhea, nausea, fever, arthralgias, and pancreatitis.[22]

Inhibitors of TNF-α

As the name indicates this class of drug act by inhibiting the TNF-α, this is responsible for the regulation of immune cells and can cause inflammation, replication, it also responds to IL-1. Drugs included in this class are adalimumab, infliximab, and golimumab. If we talk about adalimumab anti-TNF-α antibody, in recent time approved by US Food and Drug Administration for effective in moderate-to-severe UC and the side effects include chest pain, diarrhea, hives, vision problem, numbness, and itching.[23]

Herbal drugs

Herbal is beneficial having less side effects such as bovine colostrums, Butyrate Tormentil, Slippery elm, and Liquorice. In the case of Butyrate, it plays a major role in the regulation of gut homeostasis, control of inflammation, mucosal lesion, and cellular proliferation.[19] Bovine colostrums are rich in proline-rich polypeptides (PRPs) that have shown results in a patient with inflammation linked with an autoimmune disorder. PRPs diminish the activity of tumor factor and cause rejection of tumor. Colostrums consist of many immunoglobulins, IFN, and cytokines, which will enhance the immunity, and prevent illness.[24] Certain herbal drugs are very common to treat UC, i.e., *Aloe vera*, *Boswellia serrata*, Clicorice, Slippery elm (*Ulmus fulva*), wheat grass (*Triticum aestivum*), curcumin, germinated barley foodstuff, and bromelain.

Self-care treatment

The prevention is always better than cure, so we have to set daily diet routines enriched with sufficient protein, carbohydrate, and little amount of fat for the smooth functioning of body. In the case of UC doctors advise to modify their diet to help and manage symptoms of the disease. Probiotics also play a beneficial role in UC, discussed later. Depending on nutritional status, multivitamins may be recommended by

the doctor. These efforts will cure the basic symptoms of UC, i.e., diarrhea and abdominal pain. The following points should be in consideration by people with UC.[25]

- Try to eat in small portions.
- Stay hydrated by drinking water throughout the day.
- Avoid spicy food, always prefer soft food.
- Avoid the food which is rich in fiber (such as nuts, seeds, bran, and beans).
- In case of lactose tolerance limit milk products.
- Avoid consumption of alcohol and caffeine.

PROBIOTIC AS CRUCIAL LEAD

Probiotics

These are living or killed microorganism, which are beneficial for health by preventing from a diseased state. Basically, they are a part of gut microbiota but due to some intestinal problem, the concentration of probiotic from microbiota goes reduced. Hence, to attain a particular level, probiotics are given externally in various dosage forms to treat IBD.[26,27] Majorly used probiotic class is lactobacillus and *Bifidobacterium*. Probiotics are used in freeze-dried and dairy products, also available in powder, tablet, and capsule. Probiotics are also combined with herbal supplements to attain the synergism effect against IBD. As per the recent findings, probiotics act as antibacterial, immunomodulator as well as an intestinal barrier by regulation of microbiotica flora.[28,29]

Curable effect of probiotics in UC

In 2003, the first trial of VSL#3 was done on 25 patients with UC taken randomly to provide VSL#3 combination. The results showed that there is a reduction in the inflammation process by enhancement in FOXP3 mRNA expression. VSL#3 in combinations of various probiotics include living strains of: *Bifidobacterium* (*Bifidobacterium prever*, *Bifidobacterium infantis*, and *Bifidobacterium longum*), and *Lactobacillus* (*Lactobacillus casei*, *Lactobacillus acidophilus*, *Lactobacillus delbrueckii*, and *Lactobacillus plantarum*).[30] One more combination of probiotics was studied by Tsuchiya and their team named as Supply Chain Management-III. It consists of living strains of *L. acidophilus*, *Lactobacillus helveticus,* and *Bifidobacterium* sp. and the results showed the improvement in abdominal pain and bowel infection.[31] *Bifidobacterium* and lactobacillus species are mostly used, 70 patients with UC are randomly selected, they divided it into three different treatment groups and provided: Group (1) *B. bleve* BRO, *L. plantarum,* Group (2) *L. plantarum* LPO1, *L. acidophilus* LA02, and Group (3) Placebo. The results showed a decrease in severity of disease, after 2 weeks of observation significant reduction in the symptom of UC was reported.[32] Steidler and Neiryncy performed a study using recombinant technology, *Lactococcus lactis* was engineered for the secretion of IL-10, given to mice with experimental IBD, mechanism showed, the action of probiotic was similar to a steroid. American college of gastroenterology was conducted, study shows that the effect of single and combinational use of probiotics, team suggested, and single probiotic was not sufficient to cure IBS, but in the combination of two or more probiotic it synergized the effect of each other. The combination of *Lactobacillus* and *Bifidobacterium* gives a positive result in IBS.[33] On the basis of recent finding, rare studies are available in the treatment of IBS with probiotics; most of the probiotic research is associated with IBD. These studies explore the beneficial effects of probiotic in IBS also. In some studies, prebiotics are combined with probiotics to enhance the potency of formulation. The combination of prebiotic and probiotic is known as synbiotics.

Definition	
Prebiotics	These are non-digestible food ingredients
Probiotics	These are living/killed microorganism
Synbiotics	These are combination of prebiotic and probiotics

Probiotics boost up the stability of tight junction where probiotics have a different positive effect on epithelial barrier; with the help of tall receptors signally by increasing the production of Iga-cells the permeability of intestinal pathogen is decreased. Probiotics are also helpful in intestinal dysmotility.[34]

Basic property of probiotics during selection for treatment of UC

It should not be toxic. It should have the efficiency to survive in intestine, must have minimum colony-forming unit count, which makes it potent. It should remain effective during the time of storage. All probiotics are not equally active; on the basis of their studies, they can be used in combination form to obtain more results.[35]

Mechanism of probiotics in UC

Prevention of pathogen binding; probiotics inhibit the adherence of pathogen to intestine cell line; hypothetically, it produces a lining on the intestinal mucosa. Probiotics crimp the growth of pathogen bacteria and maintain intraluminal fermentation with the secretion of defensins and signal transductor (NF-KB).[36] The role of probiotics in UC is explained in Figure 2.

Enhancement in barrier function

Probiotics are studied to enhance their effective barrier function; probiotics VSL#3 can protect the intestinal mucosa by enhancing barrier function. Tight junction protein was screwed by activation of F-38 and regulated protein kinase signaling.[37] Probiotics exhibit an anti-inflammatory effect; previous findings show the deduction in the pro-inflammatory

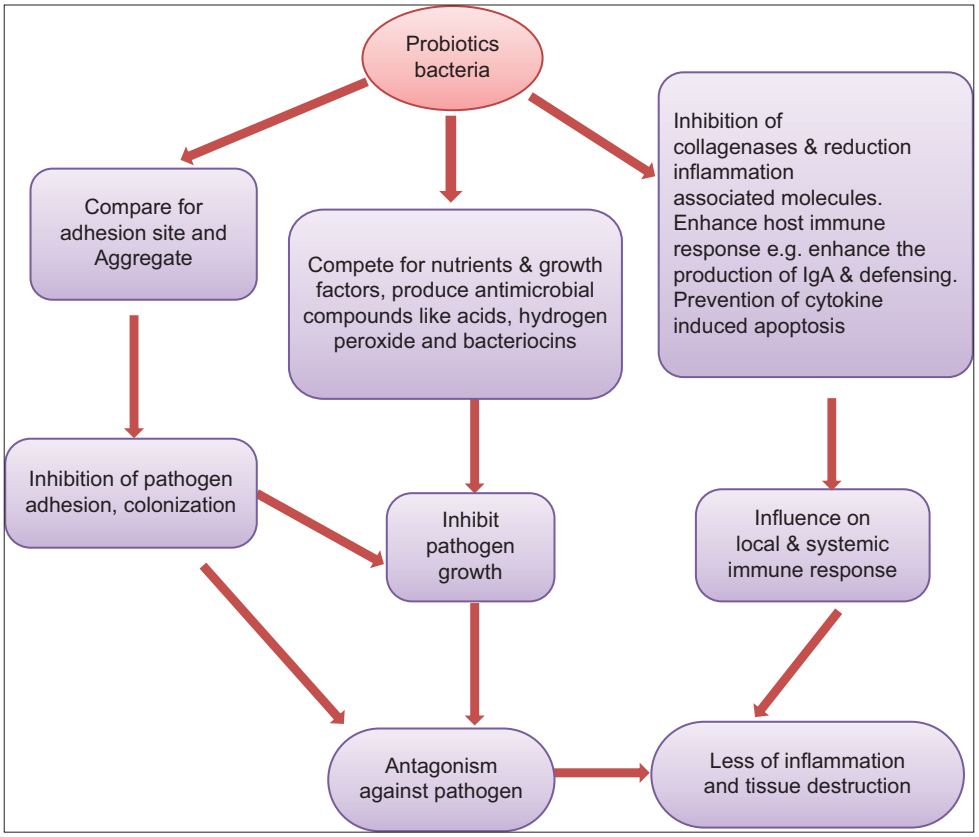

Figure 2: Role of probiotics for the treatment of ulcerative colitis

cytokines. Strains of lactobacillus cause inhibition of TNF-α with incite product of IL-8.[38]

List of marketed probiotics

There are many probiotics available in the market. Few of which are mentioned below: Florajen (*L. acidophilus*), Florajen 3 (*B. infantis*/*L. acidophilus*), *Acidophilus* (*L. acidophilus*), VSL#3 (*B. infantis*/*L. acidophilus*/*Streptococcus thermophilus*), Florastor (*Saccharomyces boulardii* lyo), RisaQuad (*L. acidophilus*), etc.

CONCLUSION

The use of probiotics in UC leads to increase in the health of the intestine and used to block or manage intestinal disorders by preventing the induction of inflammatory reactions. As a matter of fact, Indian probiotic market is valued at $12 million in 2011, is expected to witness a compound annual growth rate of 11% by 2016. Probiotics are cheaper than conventional drug therapies, improbable to enhance the incidence of antibiotic resistance and they help to manage intestine. A combination of probiotic with herbal drugs could be a realistic approach with negligible side effects. Furthermore, these strategies can provide therapeutic beneficence to colitis suffered patients.

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