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Bacterial consortia-The latest arsenal to inflammatory bowel disease bacteriotherapy

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ABSTRACT

The microbiota based dietary interventions have emerged as an unconventional bacteriotherapeutic approach for the treatment of a plethora of pathological conditions including inflammatory bowel disease. The potential side effects associated with the use of probiotics include systemic infections, deleterious metabolic activities, excessive immune stimulation in susceptible individuals and gene transfer. Moreover, probiotic strains are not very specific in offering health benefits and it is generally considered that a group of such bacteria are more effective than a single strain. Based on this assumption, fecal matter transplantation was proposed as a better alternative. Despite proving to be very effective in certain diseases, fecal microbiota transplantation has not found wide acceptability because of its poor aesthetic appeal, associated risk for infection transmission, and challenges in standardization and regulation policies. Bacterial consortia, however, emerge as multi-strain, more specific biotherapeutic agents with known composition of probiotics that are free from any risk for infections or uncertain metabolic processes. These are a group of complex microbial communities having ecological interactions among themselves. While offering therapeutic profile similar to fecal matter transplantation, bacterial consortia are free from the associated side effects. Bacterial consortia have demonstrated significant effectiveness in treatment of irritable bowel syndrome. Inflammatory bowel disease represents multifactorial inflammatory ailments comprising of both ulcerative colitis and Crohn's disease. It is generally attributed to disturbance in immunological and environmental factors while genetic factors are also known to play their role. Among all of the above, changes in gut microbiota (dysbiosis) is the main causative agent in etiology of inflammatory bowel disease. Therefore, changing the composition of microbiota through bacterial consortium offers a realistic option for treatment of inflammatory bowel disease. In this review, we decipher the relationship between dysbiosis and pathogenesis of inflammatory bowel disease. We also discuss various challenges regarding the use of bacterial consortia as inflammatory bowel disease therapy. Diving deeper, the pre-clinical and clinical studies conducted hitherto are also described. The potential and limitations of this emerging biotherapeutic approach are also discussed. Considering the worldwide prevalence of inflammatory bowel disease and constant struggle to find a safe, economical and convenient cure for it, bacterial consortia could be an attractive strategy.

1. Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is a chronic inflammatory condition of gastrointestinal tract (GIT) [1]. Though, both CD and UC share many common characteristic features, like chronic remitting, relapsing course, being inflammatory in nature, and unknown causes, they can be distinguished by the differences in genetic predisposition, risk factors, as well as clinical, endoscopic and histological features [2,3]. Also, UC is mainly confined to colon, starting from rectum and extending up to the proximal parts, while CD involves transmural skip lesions throughout the GIT and may also affect terminal ileum and colon [4]. Although, the exact cause of IBD still remains indistinct, it is widely accepted that a number of factors including gut microbiota dysbiosis, immunological abnormalities, genetic predisposition, and environmental factors contribute to the pathogenesis of the disease [5,6]. Gut dysbiosis characterized by an imbalance between protective and harmful microbiota, is considered to be a major contributor involved in the pathogenesis of IBD [7]. Gut dysbiosis associated impaired immune response along with mucosal barrier dysfunction leads to the activation and translocation of

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various pro-inflammatory cytokines such as interleukins (ILs), tumor necrosis factor (TNF), which are responsible for inflammation and progressive damage of GIT [8,9]. The detailed pathophysiology of IBD has been represented in Fig. 1.

The current treatment strategy aims to control inflammation besides decreasing disease progression and relapse, and is partially achieved by use of drugs belonging to the class of aminosalicylates, thiopurines, corticosteroids, folic acid antagonist, immunomodulators and biological agents [10]. Although, these therapeutic agents are effective in providing symptomatic relief in the early stages, their long-term use increases the risk of development of resistance and intolerance to these agents [11]. As the imbalance of gut microbiota is considered to be primarily responsible for the development of IBD, the maintenance of gut homeostasis by the use of probiotics, prebiotics, postbiotics and fecal microbiota transplantation (FMT) has been extensively explored in the past few decades. Moreover, the use of probiotic mixture, also known as probiotic or bacterial consortia, is reported to be more effective than single probiotic strain in few studies [12]. The present review comprehensively analyzes the efficacy of bacterial consortia developed so far for the treatment of IBD. Also, the challenges associated with their use and future perspectives are also discussed [13,14].

2. Relationship of host and intestinal microbiota

The human gut harbours the most complex and diversified species of trillions of microorganisms, including bacteria, virus, fungi, archaea and eukarya [15]. These complex genomes of bacteria and other microorganism that colonize a distinct milieu inside body along with their products constitute the microbiome [16]. These microorganisms are present at various sites of human body such as gut, skin, lung, colon, vagina, airway, and oral cavity. Among all, gut microbiota carries more than 150 genes alone and is therefore, considered as an essential organ. Further, it has been noted that gut microbiota is involved in many biological processes in host including growth, metabolism, development of epithelial layer and influencing innate immunity [17]. Also, gut microbiota begin to colonize during childbirth or even at early stages of fetus development. The gradual transition in gut microbiota composition takes place until the age of 2–3 years [18]. The early gut microbiota acquisition is mainly influenced by factors such as mode of delivery, preterm birth, siblings, gestational age, birth weight and use of antibiotics [19]. The gut microbiota and their metabolites exert a significant effect on host health, as well as in the etiopathogenesis of various diseases. Microbiota are localized both on the surface as well as in the various region of human body, and depending upon the anatomical site, they can be classified as gut, skin, oral, and respiratory microbiota. Gut microbiota lives in symbiotic relationship with host and plays an important role in various physiological functions, including maintenance of homeostasis and regulating immune function [20,21]. Dysbiosis of gut microbial population by antibiotic therapy, smoking, alcohol consumption, or infection influence the bidirectional relationship between host and microbiota leading to the pathogenesis of various diseases including IBD [22–24]. In addition to gastrointestinal disorders, the role of gut microbiota in neurological and skin diseases via gut-brain axis and gut-skin axis have also been investigated extensively in last one decade [33]. Microbiota gut brain axis is a bidirectional communication between gut microbiota and central nervous system; hence composition of microbiota is directly involved in pathophysiology of many neuro-psychological diseases such as autism spectrum disorders, attention deficit disorder, bipolar disorder, Parkinson's disease, anxiety, depression, migraine, epilepsy, and schizophrenia [25]. Hence,

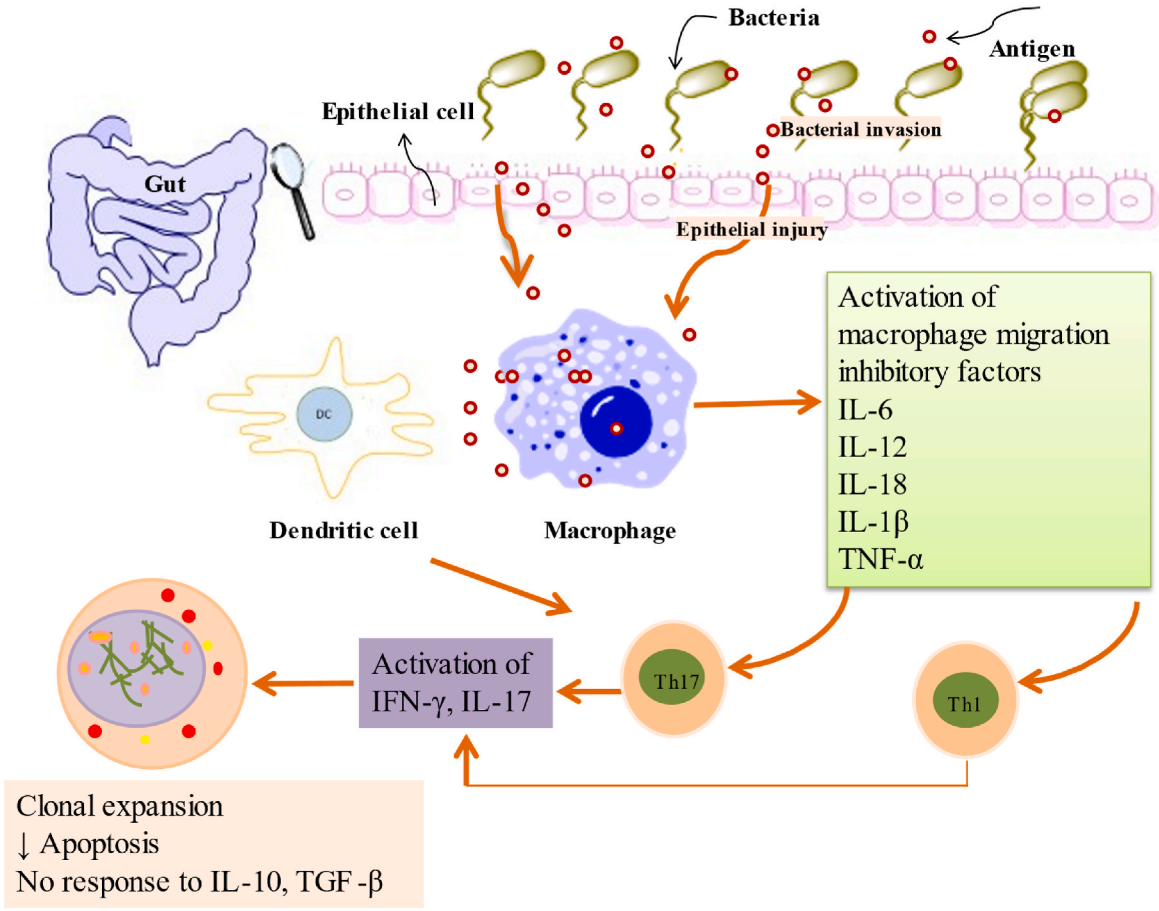

Fig. 1. Pathophysiology of IBD

modulating microbiota could be a valuable target for reducing incidences of these neurological diseases [26]. Gut derived inflammatory factors such as TNF-α, IFN-ϒ and IL-6 may enter into systemic circulation through damaged mucosal barrier, which further promote secretion of glucocorticoids resulting in increased production of pro-inflammatory cytokines, Th17 and natural killer cells initiating the process of neuroinflammation, and participate in progression of brain diseases [27]. Thus, harnessing the microbiota could emerge as a promising therapeutic option to treat central nervous system disorders [28].

Immune system of the body possesses physical and chemical barriers against pathogenic microorganism and separates microbiota from immune cells. However, under certain conditions, the commensal microorganisms start interacting with various body systems and trigger disease progress [29]. Further, microbiota helps in induction of immunological tolerance against various pathogens *via* multiple mechanisms, suggesting the role of gut microbiota commensals in induction of peripheral tolerance [30]. Presence of regulatory T cells (Treg) in gut contributes in maintaining tolerant environment and also inhibits unnecessary inflammation [31]. Polysaccharide A produced by symbiont *Bacteroides fragilis* (present in healthy gut microbiota) provides protection against *Helicobacter hepaticus* induced colitis in mice *via* expansion of IL-10 releasing Treg cells [32,33].

Furthermore, short chain fatty acids (SCFAs), produced by metabolism of carbohydrates by commensal microbiota, showed anti-inflammatory and anti-proliferative properties in gastrointestinal epithelium layers [34]. In addition to their protective role in GIT, SCFAs also show cardioprotective and neuroprotective properties. Beneficial role of SCFAs on brain homeostasis and behavior was evaluated in B57B1 mice suffering with psychosocial stress. Administration of SCFAs helped to relieve stress by alterations in host metabolism, behavior and increased responsiveness, reflecting the influence of gut microbiota on brain homeostasis. Thus microbiota mediated therapies can be explored in alleviating stress mediated disorders [35,36]. Many other biochemical and endogenous species such as vitamin K/B, hormones and serotonin produced by gut microbiota also perform diverse biological functions [37–39]. Further, the presence of epithelial associated bacteria i.e. *Mucispirillium* and segmented filamentous bacteria was reported to have a positive influence on production of immunoglobulin A, involved in protection against intestinal pathobionts [40].

3. Microbiota dysbiosis in the pathogenesis of IBD

Alteration in gut microbiota composition from beneficial commensal organisms to pathobionts leads to a condition known as gut dysbiosis [41]. Levy et al. classified dysbiosis into the three different sub-types, namely bloom of pathobionts, loss of microbial diversity and loss of commensals, whereas Vangey et al. divided dysbiosis into four sub-types i.e. loss of diversity, blooms of pathogens, change in keystone taxa and shift of metabolic capacity [42,43]. Altered gut microbiota leads to the dysregulation of metabolic and physiological functions of body, resulting in pathogenesis of a plethora of intestinal (IBD, coleliac disease and irritable bowel syndrome) and extra-intestinal diseases (allergy, asthma, diabetes, obesity, cardiovascular and neurological disorders) [44,45].

Composition of gut microbiota keeps on changing depending upon the GIT microenvironment. Although a diverse range of microorganism species such as bacteria, fungi, archaea, virus and yeast reside in human gut [46,47], the most predominant among them are bacterial phyla, particularly *Bacteroidetes, Fusobacteria*, *Firmicutes*, *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia*. *Firmicutes* and *Bacteroidetes* constitute almost 90% of total gut microbiota in healthy hosts while other species are present in much lower proportions [46,48]. Significant difference in composition of gut microbiome in IBD as compared to healthy individuals has been reported in a number of studies [49,50]. Reduction in α and β biodiversity, accompanied by loss of protective bacteria (*Faecalibacterium prausnitzii, Bifidobacterium* species, *Roseburae* species, *Bacteroides, Clostridium* and *Saccharomyces cerevisiae*), and selective overgrowth of pathogenic bacteria (*Gammaproteobacteria, Proteobacteria, Fusobacterium, Escherichia coli* and *Ruminococcus gnavusa*) bacteria have been observed in IBD patients in comparison to healthy individuals [51–53]. The change in gut microbiota in IBD has been detailed in Table 1.

Faecalibacterium prausnitzii, is one of the major microbiota, accounting for approximately 5% of total bacterial population of host intestine [136]. However, the abundance of *F. prausnitzii* is influenced by physiological environment of colon such as presence of cholane, pH and oxygen content [136,137]. *F. prausnitzii* is considered as one of the most important butyrate producers in intestine [138]. Butyrate plays an important role in maintaining gut physiology and serves as an energy provider to colonocytes [73]. Salicylic acid, another anti-inflammatory metabolite of *F. prausnitzii* is found in colon up to 10 μM concentration and is reported to be effective in reducing inflammation in 2,4,6-trinitrobenzenesulfonic acid (TNBS) induced colitis in mice. This is attributed to decrease in the levels of IL-8 through blockade of nuclear factor-kappa B (NF-kB) [139,140]. *Firmicutes* is another one of the most important butyrate producing genus of bacteria in gut that promotes epithelial barrier function *via* activation of transcriptional factors i.e. signal transducer and activator of transcription (STAT)3 and SP1 [141].

Different species of *Clostridium* (e.g. XIVa, IV, VI, XVIII), abundantly present in gut in the range of approximately 10%–40% of the total bacterial composition, are known as essential regulators of intestinal homeostasis. Atarashi et al. reported accumulation of Treg cells in colon by IV and XIVa clusters of Clostridium by providing an environment enriched in transforming growth factor (TGF)-β [142]. Further, the abundance of *Clostridium leptum*, the bacteria involved in fermentation of carbohydrates and production of SCFAs, was found to be significantly reduced in IBD patients than in healthy individuals, thus leading to stimulation of inflammatory cascade [143].

Beneficial roles of *Bifidobacterium* species in alleviating IBD *via* regulating oxidative stress, cytokines level and intestinal barrier functions have been reported in various studies [55,144]. The synergistic effect of *L. reuteri* Lr 5454 and *B. animalis* spp. Lactis Bl5764 strains observed in mice colitis model was attributed to down-regulation of lipocalin-2 and inflammatory mediators including IL-1β, IL-6, and TNF-α [91].

The species of genus *Pseudomonas* are reported to show both pathogenic as well as friendly potential, as few of the strains are opportunistic pathogens causing resistance to antibiotics, whereas other species help to degrade toxins and may control other recalcitrant bacteria [145]. The disequilibrium of *Bacteroides* present in gut is associated with pathogenesis of IBD as their decreased levels may reduce polysaccharide A expression, that is responsible for up-regulation of T cell growth and cytokines possessing protective effect against colitis [62,146]. Potential of *Bacteroides thetaiotaomicron* against CD was investigated using dextran sodium sulphate (DSS) and IL-10 knockout models. The results indicated a significant protective effect of *B. theataiotaomicron* against colon shortening and inflammatory mediators, and their administration, therefore could be an alternative approach for IBD [147].

A recent study has indicated protective effects of *Roseburia intestinalis,* a butyrate producer in colon, against intestinal inflammation and maintaining homeostasis, thus reducing the incidences of intestinal disorders including IBD [147].

Sun et al. investigated anti-inflammatory activity of lactic acid producing *Saccharomyces cerevisiae* in DSS induced colitis in mice and reported a change in diversity and composition of microbiota in diseased rats compared to that in control group animals. This was attributed to the suppression of macrophage pyroptosis and modulation of the microenvironment of intestinal microbiota [148].

The interaction ability of members of genus *Suterella* with intestinal epithelium showed adhesion of microorganism to membrane, with mild pro-inflammatory activities indicating their immunomodulator potential [149]. It is pertinent to note here that, the role of *Sutrerella* in alleviating UC is attributed to degradation of immunoglobulin (Ig) A rather

Table 1
Changes in gut microbiota in IBD patients.

Phylum	Family	Species	Condition	Source	Observation	References
Decreased beneficial bacteria						
Actinobacteria	Bifidobacteriaceae	*Bifidobacterium longum*	UC, CD	Colon, feces	↑ SCFAs, TJP ↓ TNF-α, IL-1α, ROS, IL-1β, IL-6, lipocalin, hs-CRP, NF-kβ, hBD	[54–58]
	Bifidobacteriaceae	*Bifidobacterium adolescentis*	UC, CD	Feces	↑ Treg, Th2, folate synthesis, IL-10, IL-4, IL-5 ↓ TNF-α, IL-6, IL-1β, IL-18, IL-22, IL-9	[59–61]
Bacteroidetes	Bacteroidaceae	*Bacteroides* spp.	UC, CD	Feces, mucosa	↑ T cell regulation, Treg	[62,63]
	Bacteroidaceae	*Bacteroides fragilis*	UC, CD	Feces, colon	↑ T cell regulation, Treg, TLR2 ↓ CCR5, IL-17	[64–67]
	Bacteroidaceae	*Bacteroides vulgatus*	UC	Feces	↓ IL-6, TNF-α	[68,69]
Firmicutes	Ruminococcaceae	*Faecalibacterium prausnitzii*	UC, CD, IBS	Feces, colon	↑ butyrate, IL-10 ↓ NF-κB, IL-8, IL-12, IFNγ, MAP3K8	[70–74]
	Lachnospiraceae	*Roseburia hominis*	UC, CD	Feces, ileum, colon, cecum	↑ T cell, butyrate, TLR5, Treg, fragellin	[75–77]
	Clostridium	*Roseburia intestinalis*	UC, CD	Colon	↑ Treg, TGF-β, TSLP, IL-10 ↓ Th17, IL-17, IL-6, STAT3	[78–80]
	Veillonellaceae	*Dialister invisus*	CD	Feces	↑SCFAs	[81,82]
	Ruminococcaceae	*Ruminococcus albus*	CD, UC	Colon, ileum, Ileucolon	↑ acetate ↓ TNF-α	[83–85]
	Ruminococcaceae	*Ruminococcus bromii*	CD	Feces	↑SCFAs, polysaccharide degradation	[60,86]
Proteobacteria	Sutterellaceae	*Suterella wadsworthensis*	UC	Feces, colon	↑IL-8, TLR4 ↓ TNF-α, IgA	[87–90]
Lactobacillus	Lactobacillaceae	*Lactobacillus reuteri*	UC, CD	Colon	↑ Treg, Lipocalin ↓ IL-6, MPO, IL-1β, COX-2, TNF-α, IL-17, IL-22	[91–94]
Increased pathogenic bacteria						
Proteobacteria	Enterobacteriaceae	*Escherichia coli*	CD, UC	Feces, ileum	↑ TNF-α, IFN-γ, IL-10, IL-12, IL-6, IL-23, IL-17 ↓ TLR5, IL-8	[95–99]
	Enterobactericiae	*Klebsiella pneumoniae*	CD, UC	Colon, intestine	↑ TNF-α, NO, COX-2, IL-6, IL-1β, NF-kβ, Th17 ↓ Th2, IL-4, IL-5, IL-13	[100–103]
	Pseudomonadaceae	*Pseudomonas fluorescens*	CD, UC	Feces	↑ T cell superantigen, epithelial cell damage	[104,105]
	Enterobacteriaceae	*Salmonella enteric (Typhi & Paratyphi)*	CD, UC	Rectal biopsy, stool	↑ IL-6, IL-1β, IL-18, NF-kβ, Nod1, Nod2	[106–108]
	Campylobacteraceae	*Campylobacter concisus*	CD, UC	Feces, colon, saliva, intestinal biopsy, colonic biopsy	↑ IL-1β, IL-18, TNF-α, NF-κβ, IL-6, IL-8, TLR3, IL-12, IFN-γ	[109–113]
	Campylobacteraceae	*Campylobacter jejuni*	CD, UC	Feces, colon, ileum	↑ IL-1β, IL-6, IL-8, IL-12, IL-25, TNF-α, NF-κβ, caspase 1, caspase 9 ↓ TLR9, Th-1	[114–117]
	Desulfovibrionaceae	*Bilophila wadsworthia*	UC	Colon, Feces	↑ IL-17, IL-23, IFN-γ, Th1	[118–120]
	Desulfovibrionaceae	*Desulfovibrio Spp. (D. piger, D. pigra, D. fairfieldensis, D. sulfuricans, D. vulgaris)*	UC	Feces, colon	↑ Hydrogen sulphide	[121–123]
Ascomycetous	Saccharomycetaceae	*Kluyveromyces marxianus*	UC, CD	Colon cell lines	↑ IL-10, IL-17, IL-6, IFN-γ, ROS, IL-1β, TNF-α ↓ Treg	[124–126]
Firmicutes	Clostridiaceae	*Clostridium difficile*	UC, CD	Feces	↑ TNF-α, IL-6, IL-8, IL-1β, LTB4, IFN-γ	[127–130]
	Lachnospiraceae	*Ruminococcus gnavusa*	CD	Bone marrow, feces	↑TNF-α, TLR4	[131,132]
Actinobacteria	Coriobacteriaceae	*Atopobium parvulum*	CD	Colon	↑ Mitochondrial dysfunction, hydrogen sulphide	[133–135]

CCR5: C–C chemokine receptor 5; CD: Crohn's disease; COX: Cycloxygenase; CRP: C-reactive protein; hBD: Human beta defensins; hs-CRP: High sensitivity C-reactive protein; IBS: Irritable bowel syndrome; Ig: Immunoglobulin; IFN: Interferon; IL: Interleukin; LT: Leukotriene; MAP3K8: Mitogen-activated protein kinase kinase kinase 8; MPO: Metallic peroxide; NF-kB: Nuclear factor kappa beta; NO: Nitric oxide; Nod: Nucleotide-binding and oligomerization domain; ROS: Reactive oxygen species; SCFAs: Short chain fatty acids; STAT: Signal transducer and activator of transcription; TGF: Tumor growth factor; Th: T helper cells; TJP: Tight junction potein; TLR: Toll like receptor; TNF: Tumor necrosis factor; Treg: Regulatory T cells; TSLP: Thymic stromal lymphopoietin; UC: Ulcerative colitis.

than inhibition of inflammation [87].

Lactobacillus species such as *Lactobacillus fructosus* are reported to attenuate the *Streptococcus typhimurium* SL1344 induced damage of intestinal epithelium through reduction of expression of IL-8, phosphorylated extracellular signal regulated kinase (p-ERK) and c-Jun N-terminal kinase (p-JNK) [150].

The SCFAs (acetate, propionate, butyrate, formate, and succinate) produced by various species of genus *Eubacterium* are reported to maintain gut health by promoting regulatory T cell functions [151].

Similarly, *Dialister invisu* is capable of producing acetate and propionate and any reduction in its levels leads to pathogenesis of IBD [152]. All these studies suggest that dysbiosis results in exaggeration of inflammatory response, eventually leading to IBD, *via* down-regulation of crucial anti-inflammatory mediators, apart from favoring development of pro-inflammatory mechanisms. Inflammation itself contributes to microbial imbalance, setting in a vicious cycle. As, the inflammation and dysbiosis are closely related, the therapeutic strategies aiming to re-establish eubiosis seems to be the next frontier for treatment of

inflammation mediated disorders such as IBD.

4. Bacterial consortia

Probiotics have emerged as the first line bacteriotherapeutics and are still the most popular choice in the category of pharmaceutical and nutraceuticals products. However, their viability during transition through gut, specificity for diverse pathological conditions, safety in immunocompromised patients, especially those on chemotherapy etc. are some of the challenges of probiotic therapy, leading to the exploration of better bacteriotherapeutic approaches [153]. Prebiotics, which are a group of nutrients that are degraded by gut microbiota have also been widely studied in the treatment of IBD [154]. However, their clinical use as a stand-alone therapy is limited by their lack of targeted functions, production of certain harmful fermentation products like phenolics, amines and ammonium compounds, and side effects like intestinal discomfort [155]. FMT though found to be extremely useful, has not been widely accepted because of unappealing aesthetics, risks of infection, and challenges in standardization and regulation policies [156]. Bacterial consortia emerged as more specific and acceptable therapeutic agents with known microbiological composition by virtue of which they are free from any risk for infections or uncertain metabolic processes [157,158].

Microorganisms are found intrinsically in biogeochemical cycling, where groups of different species stay together for their survival and prosper in complex microorganism communities known as microbial consortia [159]. The ecological interactions among the different species have profound role in defining shape as well as functions of the community. The microbial consortia are considerably more efficient in performing complicated functions than the individual strains due to synergistic interactions like cycling of nutrients and removal of inhibitory products [160,161]. Also, the growth in mixed culture helps to exhibit more resistance and allows more flexibility to individual strains towards environmental changes [162]. By virtue of these properties, the concept of microbial consortia has gained popularity in developing resilience and cost-effective biotechnology products, where synthetic consortia are produced to achieve desired functions performed cooperatively by mixing two or more microbial species [163]. However, evaluation criteria of microbial consortium depend upon type of bacterial strains, purpose of use, environment, stability and degradation at required pH and physicochemical parameters.

The bacterial consortium exerts anti-inflammatory and anticolitic effects *via* different mechanisms that mainly depend upon type of microorganism species. Also, bacterial consortium helps to down-regulate the level of pro-inflammatory cytokines including IL-1β, IL-6, IL-8, IL-17, IL-22 TNF-α, T helper cells (Th)1 Th2, Th17 and IFN-γ, which are highly expressed in inflammatory conditions. In addition, it also reduces levels of vascular endothelial growth factor (VEGF), TGF-β, and matrix metalloproteinase (MMPs) i.e., MMP-2 and MMP-9, thus helping to ameliorate colonic fibrosis [164,165].

The idea of treating IBD by restoring gut microbiota using microbiome-based intervention has long been well documented, indicating the effectiveness and safety, with higher cure rates [166]. Therefore, the use of bacterial consortia in treatment of conditions associated with gut dysbiosis such as IBD, irritable bowel syndrome (IBS), hyperammonemia and diabetes was also explored [167]. The biggest challenge regarding use of natural consortia is inter alia safety, quality control, reproducibility and standardization, as high level of diversity and variability in microbial composition is observed among donors. Further, the occurrence of infectious agents (*Helicobacter pylori*, *Campylobacter*, HIV, *E. coli* and *Salmonella typhi*) may qualitatively and quantitatively exaggerate a significant risk of patient safety [168]. Therefore, the trend moved towards production of genetically modified bacterial strains using re-engineering techniques. These are considered to be safer, more reproducible and reliable therapeutic agents for treatment of plethora of diseases as compared to their natural couterparts [157,169].

4.1. Animal studies demonstrating the role of bacterial consortia in IBD

Though the role of bacterial consortia in treatment of UC has been very well explored, a few studies claiming the efficacy of mixed strains in alleviating CD have also been documented. The efficacy of consortium GUT103 (strains of genera *Bacteroides*, *Akkermansia*, *Clostridium*, *Faecalibacterium)* and GUT108 (strains of *Clostridium, Intestinimonas, Bitterella, Barneseilla*) was evaluated in colitis induced in germ free mice by inoculation with pathobionts i.e. *E. coli*, *Enterococcus faecalis* and *Ruminococcus gravus* (EER). The reversal of established experimental colitis and inflamed colon was achieved after administration of GUT103. However, more profound effects were observed with GUT108. The possible modes of action of GUT103 and GUT108 in treating inflammation include activation of IL-10 immune system, down-regulation of inflammatory cytokines (IL-6 and TNF-α) and potentiation of synthesis of indole-3-acetic acid and indole-3- propionic acid. Furthermore, no toxic effects have been reported after application of GUT103 and GUT108 [158].

In another study, beneficial effect of consortium consisting of *Bacteroidetes, Fusobacteria, Proteobacteria, Actinobacteria* and *Firmicutes* species in TNBS induced colitis was estimated in male Wistar rats. A significant improvement in histological score and reduction of myeloperoxide were reported in consortium treated rats compared to control (saline) and antibiotic (ceftriaxone) group animals. The levels of bacterial bands were improved even after 10 days of treatment in both antibiotic and consortium treated animals; however, the level was significantly enhanced in consortia group (14.33 ± 1.67 vs. 17.33 ± 1.33). Also, the microbiota diversity was re-established to normal on 24th day of treatment, indicating the potential of this consortium to treat inflammation mediated conditions such as IBD [170].

Similar findings were reported by Caballero et al. indicating the efficacy of consortium of four different strains in alleviating colonization induced by vancomycin resistant *E. faecium* [171]. In another study, similar results were reported indicating the ability of a consortium of commensals against intestinal colonization promoted of vancomycin resistant *E. faecium via* up regulation of innate Toll-like receptors (TLR) and IL-6 [172].

The dual nature of *E. faecalis* as opportunistic pathogen and an important member of gut microbiota makes this microorganism a candidate of study for checking interactions with pathogenesis of IBD. The bacterial consortium (SIHUMI) consisting of strains of *E. coli*, *E. faecalis*, *R. gnavus*, *B. vulgatus*, *F. prausnitzii*, *L. plantarum*, *B. longum,* helps to reprogram the colitogenic activity of *E. faecalis* by modulating the gene expression due to co-colonizing microbes *via* ethanomaine utilization, and has been proposed as alternative approach for treatment of colitis [41].

The bacterial consortium BMC322 was designed for the reduction of inflammation and disease progression index in IBD. Results from functional microbiome investigation showed few of specific strains comprising BMC 322 consortium were reported to exhibit anti-inflammatory activity and maintain intestinal barrier integrity. Shortening of the recovery time and decrease in disease activity index by administration of BMC332 in DSS induced colitis in mice confirmed its role in treatment of IBD [173].

In a similar study, bacterial consortium transplantation was evaluated in DSS induced colitis in mice. The results indicated significant up-regulation of IL-17A, resulting in higher release of gamma delta T cells (γδ T cells) in lamina proporia section of colon that was involved in changing microbial composition of intestine. Further, the IL-17A resulted in more secretion of TLR2 and caused recovery of disrupted occluding subcellular locations [174]. Furthermore, it is reported that microbial combination produces higher amount of butyrate than individual strain which down-regulates expression of pathogen triggered proinflammatory mediators such as IL-8 and TNF-α that exaggerate

cytokines in inflamed tissue. Therefore, consortium exerts anti-inflammatory effects in IBD [175].

The corroboration of beneficial potential of bacterial consortium in CD is derived from small and uncontrolled studies only. The efficacy of GUT103 and GUT108 against EER induced colitis (similar to human Crohn's disease) was studied in IL-10 deficient mice and reversal of inflammation and restoring intestinal homeostasis, justified its role in treatment of IBD including CD [158]. The enhanced production of Treg cells in mice after administration of consortium (17 different strains of Clostridium) improved microbial diversity [176].

4.2. Human studies demonstrating the role of bacterial consortia in IBD

A number of studies have been reported indicating usefulness of different preparations of bacterial consortia in treatment of IBD in humans. Some of these studies along with important clinical trials are presented.

Various randomized controlled trials have also been conducted on the use of multispecies bacterial consortia to treat UC. From total of 36 active UC patients with refractory pouchitis, 20 were administered with consortium and 16 with placebo, with a dose of 6 g of consortium (VSL#3) daily for 1 year or until relapse. The remission was induced in 85% (17) patients treated with VSL#3 compared to 6% (1 patient) in placebo group. It is important to mention here that both placebo and VSL#3 groups were pre-treated with combination of antibiotics (metronidazole and ciprofloxacin) that induced remission in patients, which was further maintained by consortia for improved quality of life. Also, long-term use of VSL#3 was found to be safe with minimal side effects of GIT disturbance in one patient [177]. Similar results were observed using VSL#3, twice daily for 12 weeks in UC patients and results indicated significant difference in rate of remission with VSL#3 (51.9%) as compared to placebo treated group only (18.6%). Further, VSL#3 showed significant decrease in UC disease activity index when compared to placebo, presenting it as a promising safe therapeutic option to achieve clinical response in mild to moderate UC [178].

The phase 1b study on safety and efficacy of MET-2 (consortia of human commensal bacteria derived from healthy donors) was performed in patients with active UC. MET-2 was administrated as loading dose of 5 g (10 capsules) orally for 4 days, followed by 1.5 g (3 capsules) daily or loading dose of 10 g (20 capsules) orally for 4 days, followed by 1.5 g (3 capsules) daily. Amelioration of mucosal inflammation by different doses of MET-2 was achieved in UC patients along with restoration of gut microbiome [179]. Another phase 1 clinical trial was conducted to evaluate the safety, tolerability and microbiome dynamics of SER-287 (Eubacterial spores) in subjects with mild to moderate UC. SER-287 was well tolerated with minor infection and musculoskeletal tissue disorders and showed 6.7% GI colitis worsening in patients. Improved microbiome diversity in UC patients with 8.588% spore formation in SER-287 treated group and 9.817% in pre-treatment with vancomycin-SER-287 (once daily) treated patients and 9.13% in pre-treatment with vancomycin-SER-287 (once weekly) indicated its potential in treatment of UC [180].

Another trial on evaluating effect on behavior, psychology, diet pattern and gut microbiota of administration of intestinal microbiome on CD and UC is going on and its results are awaited [181].

5. Bacterial consortia side effects

In general, very few patients have presented minor to moderate adverse effects after treatment with consortia. These were mainly related to GIT disturbance such as nausea, diarrhea, constipation, and frequent bowel movement. Less frequently observed side effects include low grade fever, musculoskeletal, upper respiratory tract infection and mediastinal disorders. In few cases, skin lesions are observed after treatment with vancomycin and bacterial consortia [180,182]. It has been further reported that *in vivo* administration of gut bacterial consortia in Wistar rats induced replication of urolithin metabolites A and B. In addition, the consortia was well tolerated without any adverse effect on hematological and biochemical parameters except reduction in diversity of streptococcus strains, and hence could be a safe and potential treatment for clinical studies [183]. Another double-blind, phase 2 clinical trial was conducted to evaluate safety, tolerability, and efficacy of consortium (VE303) in primary *C. difficile* infection. The results are in concordance with previously reported data as minor side effects of gastrointestinal disorders and fatigue were observed with high dose of VE303 without causing serious morbidity or mortality [184]. It is also noteworthy here that microbiome shift by bacterial consortia is also associated with respiratory disease progress due to altered level of microbiome community of respiratory tract such as *E. coli*, *K. pneumoniae*, *P. pneumoniae*, *Proteobacteria*, *Fusobacteria* [185]. In rare cases, chances of sepsis and liver abscess may be observed with *Lactobacillus* strains [186] Though, some undesirable adverse effects are reported to occur, treatment of IBD with bacterial consortium has been reported as safe. Selection of appropriate strains along with in depth screening of donor may facilitate development of products that would be free from these adverse effects [12,158]. It is pertinent to note here that gut microbial species and enzymes have ability to shape drug efficacy and toxicity. Therefore, designing bacterial consortia for treating a disease may also influence drug potency through various mechanisms such as degrading or activating drug, potentiating enzymes for its their metabolism etc [187]. A randomized double blind clinical trial was performed to investigate effect of probiotic on CPT-1 induced toxicity in gastrointestinal cancer patients and no toxic effect was observed in any of patient, thus can be employed safely for treating diseases [188]. In another study efficacy of probiotic was evaluated in metastatic kidney cancer patients and results indicated that use of probiotics is having supplementary role in reducing diarrhea in patients [189]. However, long term application of microbial consortium has variable effect on host depending upon type of microbial biodiversity, age of patient as well as pathological condition. Long term safety profile (after 6 months of treatment) of microbiota suspension (RBX2660) against *C. difficile* associated diarrhea was evaluated in phase 2 clinical trial and some serious adverse effects such as non-cardiac chest pain, pneumonia, lung adenocarcinoma and respiratory failure was observed in one of the patients (2.94%) [190]. Similar results were reported in another clinical trial of RBX2660, where long term treatment i.e. 24 months after last dose of consortium administration caused seriousness, severity and causality (16.67%) [191]. In a phase 3 clinical trial wherein the safety profile of bacterial consortia, VE303 was evaluated for 24 weeks, 76 out of 79 patients reported mild gastrointestinal adverse effects like diarrhea, abdominal pain, flatulence, and vomiting. No grade 4 adverse effects or morbidity was reported [192]. Further studies of similar types should be conducted to address role of microbiota on drug efficacy and safety and enhance its usefulness in clinics.

6. Conclusion and future prospective

The bacterial consortia represent the next generation of bacteriotherapy with enhanced potential for the development of biotechnology-based products that can be successfully employed in treatment of a plethora of pathological conditions including IBD. However, like other microbiome-based therapies, challenges are there regarding its safety, efficacy, reliability and standardization due to diversity of strains and donor selection. IBD is a multifactorial complex disease which is being influenced by both host and bacterial genes. The understanding and gradual development in selection of microbial consortia for treating IBD can provide a strategy to unravel host-microbe and microbe-microbe interaction in disease pathophysiology. Various studies have demonstrated crucial role of gut microbiota in development and maintenance of inflammation and mediated conditions. Thus, bacterial consortia may offer a promising therapeutic option to restore gut microbial community to treat IBD. However, more preclinical and

clinical studies need to be performed with increased sample size and more pragmatic variables i.e. severity of disease, genotypic state and therapeutic regimen to generate significant conclusions.

CRediT authorship contribution statement

Mukta Gupta: Writing – original draft, Conceptualization. **Bhupinder Kapoor:** Writing – review & editing, Resources, Formal analysis. **Monica Gulati:** Validation, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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