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*Gastroenterol Clin North Am*. Author manuscript; available in PMC 2018 April 20.

Published in final edited form as:

*Gastroenterol Clin North Am*. 2017 December ; 46(4): 689–729. doi:10.1016/j.gtc.2017.08.002.

# Complementary and Alternative Medicine (CAM) and Next-Generation CAM (NG-CAM) Strategies for Therapeutic Gut Microbiota Modulation in Inflammatory Bowel Disease

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## SUMMARY

The human gastrointestinal tract is resident to a vastly diverse microbial consortium that co-exists through strict rules of invasion, dominance, resilience and succession. While some members possess stronger capabilities for survival than others, each one retains a genome characteristic of their bacterial denomination which subsequently determines survival and ultimately the composition of a human gut microbiome. Collective evidence advocates the concept of gut microbiota modulation via dietary compounds, with or without nutraceutical supplementation. However, consistent reports of strong individuality in responsiveness suggest that initial composition of host microbiota mediates the effect of nutrition modulation. There is also a strong potential for the interaction between mind and microbe to influence responsiveness, although mechanistic understanding of these complex exchanges remains in its infancy at best. Synthetic stool for FMT is a next-generation microbiome-therapy shown effective in treating *C.difficile* [417] which could provide a feasible alternative to current methods for patients with IBD. Nevertheless, studies investigating optimum timing for FMT administration are essential.

Animal and human studies are only starting to highlight the Pandora of interactions that endure between members of gut microbiome, their associated metabolites, dietary compounds, as well as host neurological and immune systems, all of which characteristic to each individual. Advanced research technologies have excelled the scientific evidence in support of CAM and toward generating NG-CAM systems designed for treatment of specific disease states, such as IBD. While the majority of envisioned NG-CAM strategies presently exist in their experimental and discovery phases, many show promise for future clinical application.

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**CONFLICT OF INTEREST**

All authors declare no conflict of interest.

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**Keywords**

Inflammatory bowel disease; Crohn's disease; ulcerative colitis; gut microbiota; complementary and alternative medicine; nutraceuticals; next-generation

## INTRODUCTION

Crohn's disease (CD) and ulcerative colitis (UC), both subtypes of inflammatory bowel disease (IBD), are chronic relapsing-remitting inflammatory disorders of the gastrointestinal tract associated with a deregulation of the T-cell mediated immune responses toward intestinal bacteria [1–3]. Disease pathogenesis is thought to reflect a complex interaction between genetic susceptibility, a defective immune system, host intestinal microbiota and environmental factors [4]. Despite substantial progress in our mechanistic understanding of chronic intestinal inflammation, including the integral role of enteric bacteria in disease pathogenesis, the precise cause of IBD is still unknown, and available treatment modalities for CD are not curative. Therefore, effective control of IBD, especially CD, is a realistic goal, and an ideal therapy is one that can alter the natural history of the disease in preventing complications while featuring a safe side effect profile and acceptable methods of delivery.

Intestinal bacteria are now considered to be a metabolically active 'organ' and the immunologic tone within the intestine should be that of tolerance towards the commensal bacteria, a balance maintained by the innate immune systems' ability to recognize intestinal antigens and appropriately activate or suppress T cell reactivity to these antigens. It is now recognized that primary colonization of the gut begins in utero, via the umbilical cord, introducing members of the genera *Enterocuccus, Streptococcus, Staphlococcus* and *Propinibacterium* [5], and possibly also via the placenta, introducing maternally derived microbes [6]. Further colonization, associated with infant delivery (i.e. vaginal vs cesarean) [7], is followed by a rapid escalation in gut microbial diversity during infancy, consisting of bacteria, archaea, viruses and fungi [8, 9]. 16S rRNA and whole genome sequencing have revealed microbial succession during these early years is nonrandom, potentially implying that early colonization patterns set the stage for bacterial community structures later in life [9]. Age-related factors associated with microbiota composition are of particular interest in IBD, considering the variability in age of onset [10], the phenotypic differences noted between early and late onset [10, 11], and the reality that efficacy in terms of optimum timing for fecal microbiota transplantation (FMT) is not understood.

Despite the fact that over sixty bacterial phyla exist in the world, the gut microbiome of a healthy human primarily consists of bacterial members belonging to two phyla, Firmicutes (~65%) and Bacteroidetes (~25%), thus implying strong underlying constraints in patterns of microbial colonization and succession [8, 12]. The remaining bacterial species are typically distributed among the phyla Actinobacteria (e.g., *Bifidobacterium* spp.), Proteobacteria (e.g., *Escherichia coli*) and Verrucomicrobacteria (e.g., *Akkermansia muciniphilia*), with a possible smaller presence of Fusobacteria and Cyanobacteria [13]. Non-bacterial species, such as archaea, fungi (i.e. mycobiota) and viruses (i.e. virome) also inhabit the human intestinal tract [14], with the human virome largely consisting of bacteriophages, which are

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numerous, and far more diverse than their bacterial counterparts [8]. Certain viral [15] and fungal species (e.g., *Candida albicans*) [16–19] identified within the human virome and mycobiota are shown to directly interact with the intestinal immune system and have been portrayed for their role in IBD pathogenesis [20]. Other species, such as the yeast *Saccharomyces boulardii*, appear protective against intestinal inflammation [21–24]. Notably, intestinal organisms survive in a community governed by a robustness of symbiotic and highly competitive relationships between, and within, host commensals and pathogenic populations. Current research to elucidate these mechanisms takes advantage of the significant, yet fairly recent, technological advancements in next-generation sequencing, synthetic biology, and genetic engineering techniques that are available.

Decades of literature have proposed the concept that gastrointestinal colonization, particularly early in life, plays a key role in development of immune systems and host tolerance to antigens, and it is only over recent years studies have revealed specific microorganisms can directly influence T cell development and maintenance, as well as downstream responses [25–29]. T regulatory cells (Tregs) play an essential role in maintaining gastrointestinal homeostasis through suppression of responses to pathogenic bacteria [30] and food antigens [31]. For example, specific bacterial members belonging to Clostridia [32, 33], and potentially *Parabacteroides* [34], have been identified to induce Tregs, possibly through production of the short chain fatty acid (SCFA) butyrate [35, 36]. There is also data demonstrating the induction of IL-10-producing Tregs, via polysaccharide A, a *Bacteroides fragilis* generated metabolite [37]. More recently, specific microbial populations *Clostridium ramosum*, *Bacteroides thetaiotaomicron*, *Peptostreptococcus magnus* and *Bacteroides fragilis* were identified to control expression of a distinct Rory expressing Treg subset population [38]. Animal studies have revealed segmented filamentous bacteria mediate dendritic cell activity (DCs), via production of serum amyloid A (SAA), leading to a downstream Th17 response [32, 39, 40]. At present, clinical application of microbiota modulation strategies that can target specific immune mechanisms remain forthcoming. Additional studies are essential to delineate the mechanisms by which specific microbiota and their metabolites affect immune cell subtypes, as well as the potential for other factors such as diet and medication to influence these intricate interactions.

## COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM)

Complementary and alternative medicine (CAM) refers to health-care strategies developed separately to that of Western or conventional mainstream medicine, with the term ‘complementary’ implying usage of these therapies in addition to conventional medicine [41]. In the past, many IBD professionals have avoided CAM because of a lack in supporting scientific evidence, despite reports indicating that upwards of 50% of IBD patients utilize non-conventional therapies (i.e. CAM) at some point during their disease course [42–45]. Over recent years however, the body of scientific and clinical evidence in support of CAM has increased dramatically, resulting in a high level of acceptance among medical professionals. Moreover, advanced research technologies are working to reshape the face of many CAM strategies (e.g., genetically engineered probiotics) into those of precise, next-generation CAM (NG-CAM) systems, designed for treatment of specific disease states,

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including IBD. Still, the integration of CAM/NG-CAM into any medical management plan, whether intended as short- or long-term, should be tailored to each individual patient, and performed by an experienced practitioner capable of evaluating all facets of the available evidence with regard to benefits, safety and cost [41].

In terms of gut microbiota modulation, CAM/NG-CAM approaches can be classified into one of four major groups; 1) nutraceuticals, 2) mind-microbe balance, 3) dietetic management, and 4) microbiome-therapy. Nutraceuticals refers to an unsuccessfully regulated group of food products ranging from herbals, botanicals, phytochemicals and isolated nutrients, to certain foods and beverages (i.e. 'functional foods') stocking specific health benefits based on their ingredients. Recent efforts to overcome the issue of nutraceutical bioavailability have led to advanced microbiome-triggered delivery systems and development of nutraceutical-producing bio-organisms. A growing body of evidence suggests that stress profoundly impacts gut microbiota composition and that the converse is also true, intestinal microorganisms are capable of altering host behavior. Conventionally known as the 'gut-brain axis', the mind-microbe balance infers that, to achieve optimal host response from any therapeutic agent, necessitates full consideration of the intimate communication bond between both mind and microbe. Dietetic management encompasses a wide spectrum of dietary regimes characterized by their macronutrient profiles, the nutrient composition or origin of specific foods (e.g. fiber type, gluten-free, saturated vs unsaturated fatty acids), or a combination of these. For example, elimination diets, individual fatty acids, high-fat (HF) diets differing in fat source (animal vs plant), and a range of dietary plant fibers have all been shown to impact gut microbial communities. Microbiome-therapy is primarily gathered into three major paradigms: additive, transformative and subtractive. Additive therapy involves supplementing gut microbiota with individual, or combinations of bacterial strains (i.e. probiotics), whereas transformative therapy entails modulation of the gut microbial community as a whole through fecal microbiota transplantation (FMT). These strategies are now evolving toward genetically engineered probiotic strains designed for specific mechanisms of disease, and the use of 'artificial' stool products in FMT. Subtractive therapy refers to selective elimination of pathogenic members of the gut microbiome, with recent studies exploring bacteriophages, a viral species able to kill a precise gamut of bacteria with exquisite specificity, as a potential therapeutic modality for shaping microbiota populations in IBD. Notably, specific dietary compounds have been an important tool for managing activation and biosafety of engineered organisms. Since it is impossible to cover the spectrum of CAM therapies held within the aforementioned groups, this review will focus on CAM and recent NG-CAM that interact with the gut microbiota in context to IBD.

One of the challenges drawing particular attention in the current literature is that baseline (i.e. pretreatment) composition of host intestinal microbiota, namely bacterial diversity, abundance and their functionality, may in fact predict individual responsiveness to therapeutic interventions [46–49]. For instance, one study identified microbiota gene richness at baseline as predictive of inflammatory and metabolic response, following a low-calorie diet intervention [50]. In another diet study involving caloric-restriction in obese individuals, pre-intervention abundance of *Akkermansia muciniphila* was found inversely related to degree of responsiveness for fasting glucose, body composition and subcutaneous

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adipocyte diameter [51]. However, further studies are required before individual bacterial species (or microbiome profiles) can be applied as predictive tools for treatment success.

## NUTRACEUTICALS

Nutraceuticals are foods, or food products, that provide health and medical benefits in the prevention or treatment of disease [52]. Chemically, nutraceuticals include a range of bioactive substances classified as polyphenolic compounds (e.g., curcumin, resveratrol, ellagitannins, flavenoids), isoprenoids (e.g., terpenoids, carotenoids), minerals (e.g., calcium, zinc), amino acid derivatives (e.g., indoles, choline), carbohydrate derivatives (e.g., oligosaccharides, polysaccharides), fatty acid and structural lipids (e.g., n-3 polyunsaturated fatty acids; PUFAs), and prebiotics [53]. In the United States, there is no specific regulatory framework for nutraceuticals or functional foods [54], and most marketed nutraceuticals do not require clinical trials to support efficacy claims [55, 56]. Although recognized as nutraceuticals, the probiotic arena of today has transcended as a NG-CAM in microbiome-therapy through genetic engineering technology, and thus presented accordingly in this review.

### Prebiotics

Prebiotics typically refer to selectively fermented non-digestible compounds that foster growth and activity of health-promoting intestinal microbiota [57]. A review of prebiotic fibers is available elsewhere [58]. Intestinal bacteria rapidly ferment these non-digestible fibers, producing metabolites central to gastrointestinal health such as *n*-3 fatty acids, metabolic derivatives of tryptophan, and the SCFAs acetate, butyrate and propionate [36, 59]. Ingestion particularly favors growth of beneficial species *Lactobacillus* and *Bifidobacterium*, contributing to SCFAs [60, 61]. Gastrointestinal benefits associated with prebiotics have included enhanced mucosal immunity, gut barrier integrity, and epithelial protection from pathogenic bacteria and other metabolites [60, 61]. Bacteria-derived butyrate supports barrier function through two distinct mechanisms, namely, hypoxia-inducible factor activity via increased colonic epithelial cell oxygen consumption [62, 63] and by suppression of histone deacetylases butyrate that can increase tight junction proteins [64].

Dietary components such as fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), soya-oligosaccharides, xylo-oligosaccharides, and pyrodextrins have been proposed to increase bacterial diversity [60, 65], as well as selectively enrich *Bifidobacterium* spp. in the gut [58]. During growth, intake of prebiotic fibers FOS, GOS and soluble corn fiber have been shown to increase absorption of calcium in humans and rats, enhancing bone properties through shifts in gut microbiota [66–69]. There is also evidence that soluble corn fiber increases calcium retention in older individuals who have reached peak bone mass [69], and is capable of altering functional pathways associated with macronutrient and vitamin metabolism [70]. This holds potential clinical utility in IBD considering the high prevalence of suboptimal bone density among patients [71–73]. Both animal and human studies demonstrate increased SCFAs with selective enrichment of *Bifidobacterium* following ingestion of resistant starches (RS), specifically RS1 and RS2 [74–76]. In humans, RS

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appears to predominantly elicit colonization by *R.bromii*, and promote butyrogenic species *F.prausnitzii* and *E.rectale* [77, 78]. Another prebiotic dietary fiber, germinated barley foodstuff, provides a glutamine-rich insoluble protein [79] identified to effectively increase luminal butyrate, lactate and acetate production via expansion of *Bifidobacterium* and *Lactobacillus* [80]. Clinical studies suggest germinated barley foodstuff may exert therapeutic benefit in UC patients with mild to moderate disease activity, attenuating clinical activity index and mucosal damage, through promotion of *Bifidobacterium* and butyrate-producing *Eubacterium limosum* [81–84].

Human prebiotic clinical intervention trials and effects on gut microbiota support the concept that prebiotic feeding increases abundance of certain bacteria and the production of various dietary metabolites. However, strong individuality in responsiveness is observed, underscoring the likelihood that initial composition of host microbiota can mediate effects of nutrition modulation [47]. There is also the possibility that, the structural variations found to exist between a single plant species [85], could prevent *Bifidobacterium* from degrading certain fiber structures, as bacterium may not possess the appropriate enzymes. Even so, considering the high capacity for microbial horizontal gene transfer in the human gut [86, 87], inter-individual differences would likely persist. Recently, Bindels *et al* (2015) proposed that prebiotics be redefined as non-digestible compounds that through its metabolization by microorganisms in the gut, modulates composition and activity of the gut microbiota, thus conferring a beneficial physiological effect on the host [65, 88]

## Polysaccharides

Polysaccharides refers to a heterogeneous group of structurally diverse carbohydrate molecules, many of which used by the food industry as additives to enhance viscosity and texture of foods. Carrageenans, one of the more widely used food additives, derive from several species of red seaweed (*Rhodophyceae*) and are unique in cellular structure. Microbial fermentation of carrageenans requires specific gut microbiome-encoded-enzymes, known as carbohydrate active enzymes (‘CAZymes’) [89]. CAZymes have been identified in genomes of marine microbes, but are absent in the human microbiome genome, thus humans are unable to digest carrageenan [86, 87, 90]. Interestingly, metagenomic studies have now uncovered bacterial members of the human gut belonging to the genus *Bacteroides* (e.g., *B. plebeius*) that possess CAZyme encoding genes, thus allowing breakdown of specific carbohydrates, and in turn, an additional energy source [87, 91]. This evolutionary adaptation is thought to reflect a natural horizontal gene transfer, in that, bacterial taxa, native to the human gut, have the ability to acquire genes from other microbes typically found outside of the human gut [86, 87]. The extent to which extrinsically acquired genes could influence microbial ecology of the human gut warrants further investigation, especially considering the rising consumption of various traditional seaweeds, such as nori (species of red algae genus *Porphyra*), traditionally used to prepare sushi throughout many nations outside of Asia.

**Squid ink polysaccharide—**Mouse models of chemotherapy have reported biological activities of squid ink polysaccharide to include anti-tumour, antioxidant, and anti-coagulation effects, as well as enhancement of both IgA secretion and gut barrier integrity

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[92–96]. These models suggested that the polysaccharide induced beneficial effects through reversal of chemotherapy-related dysbiosis. One recent animal study reported squid ink polysaccharide decreased abundance of *Ruminococcus*, *Bilophila*, *Oscillospira*, *Dorea* and, *Mucispirillum*, bacterium known to thrive during early disruption of the colonic mucosal surface layer [97].

## Casein glycomacropeptide

Glycomacropeptide (GMP), a sialic acid rich peptide, releases in whey during cheese making, and from bovine milk, releasing approximately 10-times higher amounts in the casein component of whey (i.e. casein GMP) [98]. Glycomacropeptide is significantly rich in amino acids proline, glutamine, serine, and threonine, as well as the branched chain amino acids (BCAA) isoleucine and valine. There is evidence that certain amino acids act as precursors to SCFA synthesis [99–103]. Specifically, anaerobic bacteria have the ability to metabolize glycine, threonine, glutamate, lysine, ornithine and aspartate, into acetate, which other gut microbiota utilize to generate butyrate [99]. Threonine appears to be the most versatile as it also used to generate propionate [104, 105].

Animal models of induced colitis suggest that casein GMP may attenuate intestinal damage (morphological/histological) via NF-KB/p65 pathway inhibition [106]. Animal models also indicate that Casein GMP could mediate intestinal inflammation via the gut microbiota [107–109], with administration associated with reductions in Proteobacteria, genera *Desulfovibrio* (from 30-35% to 7%), and increases in acetate, propionate and butyrate levels (cecum) [110]. Recent data proposed that GMP exerts anti-allergenic activity via modulation of gut microbiota [111]. Specifically, the GMP-induced increase in *Lactobacillus*, *Bifidobacterium* and *Bacteroides*, attributed to increased TGG-B production and reductions in mast cells [111]. Clinical trials for active distal colitis in UC patients have reported casein GMP is well-tolerated, exerting similar disease-modifying effects to that of mesalazine [112, 113].

## Mushroom Extracts

Mushrooms are recognized for their nutritional value and insoluble fiber content, with evidence supporting their unique range of bioactive metabolite substances [114]. Other compounds include mushroom polysaccharides, all of which with prebiotic properties, such as β-D-glucan polymers, polysaccharopeptides (PSP), polysaccharide proteins (e.g., PSK), chitin, mannans, galactans, and xylans [115]. Isolation of bioactive substances requires the young fruiting body (mycelium with primordia), thus extracted before the mushroom blooms [114], with triterpenes, lipids, and phenols depicted for their immunomodulatory properties [114, 116]. Mushroom bioactive metabolites are shown to stimulate different cells in the immune system, albeit that the ability of certain metabolites promote or suppress immune systems depends on dosage, route and timing of administration, as well as how the mushroom is cultivated (i.e. soil, harvesting, geography) [114]. Nevertheless, various bioactive metabolites are in use clinically [117, 118], and are available commercially worldwide in the form of capsules, food additives, syrups or teas [117].

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In a mouse model of diet-induced obesity, administration of a water extract of *Ganoderma lucidum* mycelium (WEGL) was found to reverse HF-diet induced gut dysbiosis, noted by decreased *Firmicutes*-to-*Bacteroidetes* ratio and *Proteobacteria* levels, with a 10-fold increase in butyrate-producing species *Roseburia* [119]. The anti-inflammatory and gastroprotective effects identified were recapitulated following FMT (WEGL microbiota inoculum) into WEGL naïve recipients fed a HF-diet [119]. In a recent report, administration of *G. lucidum* (100mg/kg rat body weight, as oral suspension) improved barrier function via upregulation of occludin expression and increased ileal IgA [120]. Change in immune function correlated with improved microbiota richness, decreased *Firmicutes*-to-*Bacteroidetes* ratio and reduced relative abundance of *Proteobacteria* (cecal content). However, a 2015 Cochrane review of randomized controlled clinical trials (5 trials, N=398) investigating effectiveness of WEGL (as anti-obesity) and *G. lucidum* for treatment of pharmacologically modifiable risk factors of cardiovascular disease (CVD), did not support use in CVD or type 2 diabetes [121]. In addition, participants who took *G. lucidum* for four months were 1.67 times (RR=1.67; 95%CI 0.86 to 3.24) more likely to experience an adverse event vs placebo. Adverse effects included nausea, diarrhea or constipation.

## Phytochemicals

Phytochemicals are naturally occurring plant chemicals that provide plants with color, odor and flavor. Thousands of structurally heterogeneous phytochemical compounds have been identified thus far, many of which shown to influence chemical processes of the host, including several pathways related to IBD pathogenesis [122]. Supplementation strategies in animal models of IBD seem to ameliorate intestinal inflammation, with or without changes to gut microbiota, however, data has poorly reflected in human clinical trials [123]. Differences in study design, and reports of conflicting or harmful effects have limited generalization of findings. Details of this are outside the scope of the present review and are discussed extensively elsewhere [124–126].

Approximately 90-95% of total dietary polyphenols reach the colon unabsorbed [127]. Microbial modulation has been reported in animal or human studies, or both, by; epigallocatechin gallate (EGCG, main catechin of green tea) [128–131], ellagic acid and ellagitannis (pomegranate, raspberries, blackberries, strawberries and chestnuts) [132, 133], ginseng saponins (ginsenodises) [134, 135], and resveratrol (red wine) [136, 137]. *In vitro* evidence has shown that naringenin (a flavone) can inhibit growth and adhesion of Gram-negative pathogen *Salmonella typhimurium*, yet enhance proliferation of the anti-inflammatory probiotic strain *L. rhamnosus* [138, 139]. Recently, EGCG supplementation was shown to decrease DNA damage in mice fed a HF diet, with reversal of tissue-specific gene expression and methylation patterns of *DNA methyltransferase 1* and *MutL homologue 1*, implying potential for epigenetic consequences [140]. The ratio of *Firmicutes* to *Bacteroidetes* in supplemented mice was also significantly lower to that of controls.

The ability for phytochemicals to influence composition and metabolic activity of colonic bacteria definitely exists, but efficacy intimately reflects dosage, timing and route of administration. Bioavailability is also an important issue, and depends on phytochemical origin (whole food vs extract), overall diet composition [141], as well as host colonic

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microbiome via bacterial metabolism of dietary polyphenols, in turn affecting bioavailability and derived metabolites [122, 142, 143]. While certain colonic bacteria can enhance bioavailability of dietary [124, 143–147], recent data revealed microbial metabolism of certain phytochemicals (e.g., quercetin), could indirectly influence the effects (enhance or suppress) of other dietary compounds, such as *n*-3 PUFAs [148].

**Microbiome triggered delivery—**In an effort to overcome bioavailability issues, several groups have focused on colon-targeted delivery systems, utilizing non-digestible fibers (e.g. resistant starch) degraded exclusively by colonic microbiota, for encapsulation and delivery of bioavailable nutraceuticals [149–151]. This method of encapsulation has proven clinically effective for delivery of 1, 25-dihydroxyvitamin D3-25-b-glucuronide (hormonally active vitamin D) in treating localized colonic inflammation, without risk of hypercalcemia or intestinal loss [152, 153]. In another study, mesalamine linked with L-glutamine via azo linkage, a bond specifically cleaved by the colonic microbiome, was reported to reach 84.7% targeted drug and nutraceutical delivery in the colon [154].

Colon-targeted drug delivery systems intended for IBD patients have implemented food grade materials including soy protein, β-lacto globulin (whey), chitosan and zein [126]. To improve encapsulation and pH controlled release of nutraceuticals, smart pH nanoparticles namely carboxymethyl chitosan and calcium pectinate cross-linked with PEI, have also been established [155]. The latter coating method is degraded only by pectinases in the colonic environment, and was reported to protect resveratrol activity until desired release into the lower bowel [156]. Other colon-targeted carrier systems of curcumin have proven successful *in vivo* [157–159]. Several groups have effectively implemented co-encapsulation, essentially, two nutraceuticals in a single carrier.

Nutraceutical co-encapsulations have comprised; curcumin/resveratrol [160], curcumin/catechin [161], curcumin/piperine [162], gallic acid/curcumin co-administered with ascorbic acid/quercetin [163], curcumin/flax seed oil [164], and prebiotic/probiotic co-delivery [165]. Efforts to develop multilayered particulate drug delivery systems for controlled, sustained drug release, including co-encapsulation of drug and nutraceutical while preventing pharmacological cross-reactivity has shown immense promise as a NG-CAM approach in nutraceutical and drug delivery [126, 166].

## Medical Cannabis

Cannabinoids, derived from the cannabis plant *C.sativa*, include over 60 aromatic hydrocarbons, of which $\Delta^9$-tetrahydrocannabinol (THC) is the primary psychoactive component. The endocannabinoid system is ubiquitously expressed throughout the human and rodent body, modulating intestinal peristalsis, gastric acid secretion, hunger (including fat-rich intake) [167–169], gut barrier integrity and intestinal inflammation, with gut microbiota interactions identified [170–175]. The inhibitory effects on gastrointestinal motility may benefit patients with diarrhea and intestinal inflammation, as activation of cannabinoid receptors appears to reduce inflammation-associated hyper-motility [67, 176, 177]. Comprehensive reviews of these mechanisms are available elsewhere [41, 173].

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Epithelial cells, immune cells (B cells, NK cells, and mast cells) [178, 179], and the enteric nervous system are all cellular targets of the endocannabinoid system [169, 180–182]. Molecular targets include cannabinoid receptor (CBR) type 1 ($CB_1R$) and CBR type 2 ($CB_2R$), as well as transient receptor potential vanilloid 1 receptors (TRPV1s, best known as the receptor for capsaicin), peroxisome proliferator-activated receptor alpha (PPARαs) and the orphan G-protein coupled receptors (GPCRs), GPR55 and GPR119 [169, 183].

Endogenously derived bioactive lipids that activate CBRs include members of the *N*-acylethanolamine (NAE) family, namely 2-arachidonoylglycerol (2-AG), a promotor of gut barrier integrity, and *N*-arachidonoylethanolamine (AEA; also termed anandamide), a promotor of epithelial permeability [184], as well as *N*-palmitoylethanolamine (PEA), *N*-oleoylethanolamine (OEA), *N*-stearoylethanolamine (SEA) and *N*-linoleylethanolamine (LEA) [185]. These lipids can act as natural ligands for PPARα (OEA and PEA) [186, 187] TRPV1 (AEA and OEA) [169, 188, 189]. Other bioactive lipids belonging to the acylglycerol family, palmitoyl-glycerol (2-PG) and oleoylglycerol (2-OG), are also considered protective of barrier function [190–193].

Mechanistic studies (both *in vitro* experiments and animal models) have suggested endocannabinoids, namely $CB_1R$ and $CB_2R$ mediate gut barrier function, epithelial barrier permeability and inflammatory processes, and thus may offer protective effects in IBD [194–198]. Conversely, intestinal biopsies of UC and CD patients revealed enhanced endocannabinoid or bioactive lipid levels, with or without increased CB receptor expression, [189, 199–206] implying dysregulation of the endocannabinoid system plays a role in IBD pathogenesis. In addition, there is now evidence supporting a link between host intestinal microbiota and endocannabinoids in mediating intestinal integrity [207] .

*Lactobacillus acidophilus* was the first bacteria specifically shown to modulate the expression of CBRs and μ-opioid receptors in murine intestinal cells [208]. The effects of intestinal bacteria on CBR expression was well illustrated in an elaborate study implementing several models of gut microbiota modulation (HF-diet, prebiotics, probiotics or antibiotics), and mice bearing specific mutations involved in bacterial recognition (TLR, Myd88; myeloid differentiation primary response gene 88). Results indicated that gut microbiota modulation could activate colonic *Cnr1* expression, the gene encoding for $CB_1R$, which in turn influences gut permeability and plasma lipopolysaccharide (LPS) levels [207, 209]. Everard *et al.* (2013) observed improvements in gut barrier function correlated with increased intestinal levels of 2-PG, 2-OG and 2-AG in genetically susceptible obese and type 2 diabetic mice administered *Akkermansia muciniphila* and fed a HF-diet [207, 209]. More recently, the same group showed that intestinal epithelial Myd88 deletion in mice (IEC Myd99 KO) partially protected against inflammation and gut barrier disruption induced by a HF-diet via mechanisms directly involving gut microbiota, and that in the absence of IEC Myd88, levels of AEA decreased, whereas both 2-AG and 2-OG increased. The authors suggested that activation of GPR119 via 2-OG stimulates intestinal L-cell release of glucagon-like peptide-2, a peptide involved in barrier function [210]. Overall, crosstalk between the gut microbiota, endocannabinoid system and metabolism of the host appears capable of inducing specific changes in the intestinal innate immune system, and *vise versa*.

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In a 2011 survey conducted in Mount Sinai Hospital, Toronto Canada evaluating cannabis usage among IBD patients (N=291), 50% of CD and 33% of UC patients reported having used cannabis as a CAM method to relieve IBD-related symptoms such as pain, appetite loss and diarrhea, at some point during their disease course [211]. One retrospective study (N=30, CD) [212] and two prospective studies (N=13; IBD, N=21; CD) [213, 214] have reported beneficial effects of cannabis usage for IBD symptom control, although study limitations included lack of standardization, dosing inconsistency and diversity in cannabis plant strain. In addition, side effects ranged from addiction, dry mouth, drowsiness, increased appetite, to a sensation of “high”. To this end, authorities now forbid motor vehicle use of for at least 3-4 hours after smoking, and 6 hours post oral ingestion [215]. Studies evaluating pharmacological modulation of the endocannabinoid system are currently underway (experimental and clinical trials), but few of these account for the potential interaction between the gut microbiome or endogenous bioactive lipids [216].

Nutrition-based modulation of the endocannabinoid system tone by reducing ratio of *n*-6 to *n*-3 has proven effective in some obesity studies [217–219]. For example, docosahexaenoic acid (DHA, C22:0) administration was associated with decreased levels of AEA and 2-AG, and reductions in inflammation and fat mass in mice [220]. In obese individuals, daily supplementation with *n*-3 PUFAs from krill oil reduced plasma levels of 2-AG [217]. The implication of these findings in IBD is unclear considering the gastro-protective properties of 2-AG. Nutrition modulation of the endocannabinoid system, particularly in IBD, remains in the exploratory and discovery phase.

## MIND-MICROBE BALANCE

Numerous studies advocate the neural, hormonal and immune-related communication pathways that exist between the gut and brain of the host [221–224]. In IBD patients, various inflammatory mechanisms affecting epithelial integrity and pro-inflammatory cytokine production [225] have been proposed in explanation of the long-reported correlation between stress and increased relapse of disease [226–230]. However, it is possible that some of these proposed mechanisms are in fact consequences of altered gut bacteria, as stress has now been discovered to profoundly influence gut microbial communities [231, 232]. Yet the converse is also true, with animal models showing that changes to intestinal microorganisms can indeed lead to alterations in behavior. (For review, refer to Abautret-Daly 2017).

Additional animal studies are required and should provide and invaluable first line approach to understanding the physiological changes that occur in the brain in response to intestinal microorganisms, in context to the internal and external milieu (host-specific) that constantly shapes both microbiome and brain. To this end, maintaining the host mind-microbe balance, via an ongoing consideration of this multifaceted communication pathway, could prove quintessential in attaining maximum efficacy of any treatment modality.

## DIETETIC MANAGEMENT

Diet is recognized as one of the primary driving forces in shaping the composition of gut bacteria and metabolite production [233–235]. Notably, intestinal microbiota also play an

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important role in the synthesis of several vitamins (B-vitamins, vitamin K, vitamin A) [236, 237], and can affect the absorption of essential minerals such as iron, (Kau A 2011) magnesium and calcium in the host [238]. Literature supports dietary intervention as a means of promoting beneficial host-bacteria interactions [59, 216, 239], with new evidence revealing how single food ingredients (e.g., turmeric) can interact with functional traits of intestinal microbiota to regulate host physiology [240]. However, the potential interactions between dietary compounds and host-specific microbial communities have not been investigated in most human diet intervention studies performed to date. A recent review of the known interactions between mucosal immunity, host genetics, gut microbiome and diet is available [241].

## Macronutrients

Even small dietary changes have the potential to alter the composition of gut microbiota, in as little as a day [242, 243]. Short-term dietary interventions, especially those devoid of carbohydrates appear to have the most profound effect [233], but taxonomic changes are not consistent among individuals [235], perhaps a reflection of baseline microbiota composition. Fungal abundance has been linked to a carbohydrate-rich diet, with *candida* abundance positively correlated with carbohydrate intake, and negatively correlated with total saturated fatty acids [244]. Long-term dietary changes tend to impact ratios of *Bacteriodes, Prevotella*, and *Firmicutes*, with the most profound change in microbiota composition and bacterial metabolites resulting from diets high in red meat and fat, namely PUFAs [235, 245, 246]. Studies have suggested dietary fiber promotes *Prevotella*, whereas higher protein and fat intakes promote *Bacteroides* dominance [235, 245, 246].

In IL-10$^{-/-}$ mice, significant blooms in the ‘pathobiont’ *Bilophila wadsworthia* correlated with feeding a HF-diet rich in saturated milk fat [25]. The sulfite-reducing properties of *B.wadsworthia* led to an abundance of hydrogen sulfide production, a molecule disruptive to epithelial barrier function [247, 248]. Other animal models have shown that a HF-diet, in combination with high sugar, increases adherent invasive *E.coli* (AIEC) [249], while others show that certain fibers (pectin, guar gum) can potentially mediate the pro-inflammatory effects of a dietary lipid [250]. Various IBD mouse models have suggested medium chain triglycerides (MCTs) can exert anti-inflammatory effects, thereby reducing intestinal inflammation [251–253]. In these studies, MCTs consisted of various saturated fatty acids sourced from coconut oil.

A predominantly meat-based diet was reported to decrease *Clostridiales*, a bacterium involved in plant-based fiber metabolism, while increasing abundance of bile-tolerant *Alistipes* [233]. In professional athletes, microbial diversity is markedly impacted by disproportionately high dietary intakes of protein, particularly within the genus *Akkermansia* [254]. Animal-based foods (i.e. red meat) deliver L-carnitine to certain gut bacteria producing trimethylamine N-oxide (TMAO) [255], a molecule identified to promote atherosclerosis in animal models (Lang 1998) and humans [256]. In mice, potato resistant-starch appeared to attenuate detrimental effects of a meat-based diet, partly by promoting members the beneficial, *Lactobacillus* spp. [257, 258].

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Mediterranean diets, which are inherently low in red meat, has been suggested to beneficially impact gut microbiota [259], whereas an energy restricted diet, in combination with dietary fiber, was shown to increase microbial diversity an upwards of 25%, in individuals with low diversity [260]. Of interest, omnivores appear to produce more TMAO from dietary L-carnitine than that of vegans or vegetarians [256]. One plausible explanation could be archaeal lineages underlying the human gut microbiome. Certain strains of methanogens in the human gut, such as *Methanomassiliicoccus luminyensis* and *Methanosarcina barkeri* strictly use methyl-based compounds, including TMA, to enable their growth, thus could readily deplete TMA levels [261]. For instance, *M.luminyensis* encodes a rare proteinogenetic amino acid pyrrolysine (Pyl), a characteristic shared by few other bacteria [262]. This is a truly unique characteristic since methanogenesis of TMA (a methylated amine) is only possible in the presence of pyrrolysine in active catalytic site [263]. Notably, studies exploring the abundance and activity of archaeal taxa between human populations have identified significant differences in organism groups based on geographic location, as well as the consumption of specific food items such as salt-fermented seafood [262, 264–268].

**B-Vitamins—**The human gut microbiota supplies the host with B-vitamins, including niacin (B3), riboflavin (B2), cobalamin (B12), biotin (B8), folate (B9), thiamin (B1), pantothenate (B5) and pyridoxine (B7). The host relies largely on microbiota-derived B-vitamins, as well as those obtained from dietary sources, as human cells alone do not produce sufficient quantities of B-vitamins [269]. A comprehensive genome assessment of 256 common human gut bacteria revealed a diverse distribution in the presence and absence of B-vitamin biosynthesis pathways, as well as that gut microbes actively exchange B-vitamins among each other, and in doing so, enable organisms which are deficient in any of these vital biosynthesis pathways, to survive [236]. Three distinct genome patterns, were identified, namely; 1) Actinobacteria are limited to niacin, pyridoxine and thiamin pathways, 2) except for niacin, all pathways are lacking in six Firmicutes and two Actinobacteria genomes, and 3) five Firmicutes and three Proteobacteria genomes lack all pathways except for biotin and folate biosynthesis. Inverse patterns were also noted, implying complementary relationships between microbiota. For instance, the essential roles for folate metabolism were missing in all four *F.prausnitzii* genomes. Findings indicate that perturbations to gut microbiota may impact not only individual B-vitamin requirements, but that deficiency in one or more B-vitamin, can lead to unfavorable blooms in pro-inflammatory organisms[236]. On the other hand, supplementation strategies using single or various combinations of B-vitamins may provide a novel avenue for manipulating the gut microbiota.

**Vitamin D—**The vitamin D receptor (VDR) is abundantly expressed throughout the intestine and in all immune cells, and is both directly and indirectly targeted by the bioactive forms of vitamin D, 1,25-Dihydroxyvitamin D ($1,25[OH]_2D$ and $1,25[OH]_2D_3$) [270–272]. There is evidence to support the interaction between vitamin D, the VDR and gut microbial communities in immune-mediated disorders. For instance, compared to WT mice, VDR null mice have a depletion in *Alistipes* and *Odoribacter* with markedly increased levels of *Clostridium*, *Bacteroides*, and *Eggerthella* (cecum) [273], the latter bacterium implicated in

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UC and CD [274]. In a model of colitis-induced colorectal cancer, increased VDR expression following administration of VSL#3 was associated with lower colon damage and decreased in richness and diversity of mucosally adherent bacteria [275]. Low vitamin D status is frequently observed in IBD, especially in CD patients [276]. One randomized controlled trial reported oral supplementation with *Lactobacillus reuteri* NCIMB 30242 increased circulating 25(OH)D concentrations [277].

## Elimination Diets

Elimination diets consist of an assortment of restrictive dietary regimens entailing the avoidance of specific foods or food groups that may, or may not, precede re-introduction of single food types for identification of those that initiate symptoms. Most elimination diets are not supported by gastroenterology organizations [278–280] although approximately 70% of IBD patients report implementing some form of elimination diet while in remission [281]. Often, these self-imposed diets are based on non-medical resources, such as the internet or IBD support groups, with long-term avoidance of major food groups resulting in severe nutrient deficiencies and malnutrition [125, 282]. Recent data shows malnutrition can alter microbial composition, and intraepithelial lymphocyte phenotype of the small intestine [283].

**FODMAP—**A low-FODMAP (acronym of “Fermentable Oligo-, Di-, Mono and Polyols”) diet encompasses the dietary restriction of fermentable oligosaccharides (many kinds of vegetables including ‘onion family’, legumes, wheat/rye), disaccharides (lactose-based dairy; milk, yoghurt, cheeses), monosaccharides (many kinds of fruits, dried fruit, fruit juice) and polyols (honey, corn syrup, fructose, sweeteners ending in ‘-ol’) [284]. In principal, the diet may reduce symptoms of bloating and abdominal pain through the avoidance of short-chain carbohydrates (insoluble fibers) which undergo rapid fermentation by colonic bacteria [284, 285]. In patients with existing disease or intestinal narrowing (strictures) avoidance of high-FODMAP foods (i.e. insoluble fiber) thus may be appropriate [281]. However, the majority of excluded FODMAP foods are indeed prebiotics, capable of beneficially modulating microbiota communities [286, 287]. In IBS patients, one randomized controlled trial reported a low-FODMAP diet to significantly reduce *Bifidobacterium* spp [287], with a second trial reporting greater bacterial diversity of butyrate-producing microbiota clusters in the high-FODMAP group, and reduced total bacterial abundance in the low-FODMAP group [286]. The high-FODMAP diet increased the relative abundance of anti-inflammatory *Akkermansia muciniphila* and the butyrate-producing Clostridium cluster XIVa [286]. Oligosaccharides (soluble fiber) were reported to block adherence of pathogenic bacteria to epithelia *in vitro*, including mucosally associated AIEC, a bacterium frequently observed within the mucosa of CD patients [288, 289]. Of the soluble plant fibers, soluble plantain fiber was reported the most consistently effective, inhibiting adherence of *Salmonella* spp., *Shigella* spp, Enterotoxigenic *E.coli* and *C.difficile* [290, 291]. Many of the oligosaccharide-containing cruciferous vegetables excluded from the FODMAP diet (e.g., brussel sprouts, cabbage, collard greens, kale) are also rich in sulfur containing compounds called glucosinolates, converted by gut microbiota to biologically active, anti-inflammatory compounds such as indoles, nitriles and isothiocyanates [241, 292].

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**Specific Carbohydrate Diet (SCD)—**The specific carbohydrate diet (SCD) involves elimination of most dietary carbohydrates, primarily grains, starches, dairy, and sugars/sweeteners (except honey). Evidence to support effectiveness of SCD to induce or maintain remission in IBD is only available through small case series in CD and UC [293–296]. The proposed mechanisms underlying SCD beneficial effects include; altered macronutrient ratio (protein, fat), reduced dietary gluten intake, or reduced intake of food additives (e.g., emulsifiers), shown to influence gut microbiota and barrier function [249, 297, 298]. Animal models of gluten sensitivity support the modulatory role of gut microbiota in host responses to gluten [299], with non-celiac, gluten-sensitive IBD patients reporting improvement in clinical symptoms following a gluten-free diet [300].

### Exclusive elemental nutrition (EEN)

Exclusive enteral nutrition (EEN) is a formula based therapy recommended as first line therapy for induction of remission in pediatric CD, with 85% efficacy rate [301]. Lower efficacy is noted in adult CD patients, possibly because of poor compliance or longer exposure to immunosuppressive treatments [239]. Some pediatric CD studies show EEN-induced alterations to *Bacteroides-Prevotella* correlate with therapeutic response [302, 303] whereas less impressive changes are observed in samples of adult CD patients post-treatment with enteral nutrition [303]. There is also literature suggesting that intestinal inflammation, relative to CD, may induce some changes in microbiota, such as reduced diversity and increased Proteobacteria [288]. Taken together, additional studies assessing the effects of EEN and enteral nutrition in adult CD patients are required.

## MICROBIOME-THERAPY

Microbiome-therapy such as additive (e.g., probiotics), subtractive (e.g., selective antibiotics, nutraceuticals with anti-microbial properties), or transformative (i.e. FMT) are proving effective, although individual responsiveness varies substantially.

### Subtractive therapy

Subtractive therapy is the removal of specific bacterial species, or groups of species, from the gut to correct gut disease-associated dysbiosis, thereby restoring host microbial homeostasis. Elimination of host pathogenic gut bacteria though conventional broad-spectrum antibiotics or non-conventional nutraceutical products with anti-microbial activity [304], leads to a concomitant reduction in host commensals, possibly increasing host susceptibility to other infectious agents (e.g., *C.difficile*). Next-generation subtractive therapies have overturned the concept of therapeutic probiotics, to that of therapeutic bacteriocins, a bacterially derived antimicrobial peptide with toxic activity [305]. Metagenomic and *in vivo* efforts demonstrate bacteriocin producers have a strong competitive/fitness advantage and increased protection against pathogens [58, 306–309]. Subtractive therapy has also gone viral, via bacteriophage therapy, a subset of viral species with the potential to bind and kill a narrow range of bacteria with impeccable specificity [310–312]. Bacteriophages, or phages, are highly abundant, naturally occurring organic entities. Viral genomes have been identified in both healthy and diseased individuals [313–315], with healthy humans harboring an estimated 1200 viral genotypes [316]. Some IBD

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studies demonstrate reduced bacterial diversity with concomitant increase in bacteriophage richness, specifically in Caudovirales [314], whereas others have reported decreased overall diversity [317–319]. Intestinal virome populations seem to be unique to each individual [313, 315], and phage community structure is highly susceptible to diet [313], including other factors such as geographical location [314]. Evidence indicates that viromes are also acquired via diet [320], and it has been suggested that ingestion of viral communities occurs at a much higher rate than internal production [321].

Current efforts to enhance, or engineer bacteriophages, for host therapeutic benefit, have focused on; enzymatic dispersal of bacteria in protective biofilms [322], antibiotic resistance [322, 323], antimicrobial activity [324], and modulation of gut microbial communities via cell death [325–330]. Therapeutic deployment of bacteriophage therapy in IBD has utilized naturally occurring, or genetically engineered viral parasites [325]. Of interest, it now proposed that phages could exert immunogenic effects [331], with several studies demonstrating direct effects of intestinal phages on the immune system, inding pro- and anti-inflammatory responses [316, 332–341]. Research exploring bacteriophage therapy remains in its early stages; however, the prospective that natural or engineered phages (i.e. augmented anti-bacterial capability) can intimately control microbial population structure, while mediating mucosal immunity, offers an intriguing prospect in the management of IBD patients.

### Additive therapy

Additive therapy entails supplementation of host microbiota with either individual, or a combination of bacterial strains either natural (i.e.probiotics) or genetically engineered in origin, such as probiotic strains with enhanced function.

### Probiotics

Probiotics are live microorganisms that exert health benefits to the host when administered in sufficient quantity, with strains isolated from the human intestine suggested as preferential [310]. Animals and humans investigations of various probiotic regimens in IBD have yielded controversial results, and animal data inconsistently reflecting in human IBD trials [305]. Two strains of probiotics *Escherichia coli* Nissle 1917 and VSL#3 have shown some efficacy in UC and pouchitis [307, 342–346]; however, no recommendations exist for probiotic administration in CD. Clinical intervention studies investigating their effects on the microbiota and human health have been limited by differences in probiotic formulation, timing of administration, and dosage, as well as variability in patient diet and medication use (For reviews see: Vindigni 2016, Uranga 2016, Abautret 2017, Yadav 2016) [125, 226, 347, 348]. To date, no IBD focused research has explored the potential therapeutic benefit of probiotics in alleviating anxiety or depression, although this has been explored in other disorders [226].

### Genetically Engineered Probiotics

Recent efforts are focusing on genetic modification of probiotic strains as a NG-CAM strategy. Advantages of enhanced bio-organisms can include stability of colonization (i.e. bioavailability, longevity) and dynamic correction of disease-dysbiosis related perturbations

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to prevent or resolve inflammation [305]. Application of cellular engineering in augmentation of prophylactic probiotics such as *E. coli* Nissle 1917 and *Lactobacillus jensenii* has been successful in overcoming natural colonization resistance conferred by host resident gut microbiota [349]. Today, *Lactococcus lactis* is one of the most commonly applied bacterial chassis, a nonpathogenic, non-colonizing Gram-positive bacterium used extensively throughout the dairy industry [350]. In mice, *L. lactis* has been successfully engineered to secrete biologically active murine IL-10, a potent anti-inflammatory cytokine, relevant to IBD [350, 351]. In addition, when synthesized *in vivo*, lower doses of IL-10 were required compared to systemic IL-10 administration [351]. Phase I clinical trials using IL-10 secreting *L.lactis* have been well tolerated in CD patients, although efficacy was modest [352]. A nanobody-secreting modified strain of *L. lactis*, delivering active anti-mTNF nanobodies locally to the colonic mucosa, has proven highly efficacious in DSS-induced colitis and established enterocolitis IL-10 null mice [353]. Described for its anti-inflammatory properties, elafin is associated with restoring barrier function of damaged intestinal epithelia [354–356], with reduced expression and subsequent defective elastolytic activity reported in patients with IBD [357–359]. Two strains of elafin-secreting bacteria, *L.lactis* and *L. casei*, were shown to decrease intestinal inflammation in mice, and to protect cultured human epithelial cells from increased epithelial permeability [360]. Other modifications of *L. lactis* for treatment of diabetes and autoimmune disease [361, 362] have been investigated, namely strains-producing auto-antigen proinsulin [363] and glutamic acid [291]. Administration of NAEs directly to the intestinal lumen to promote endocannabinoid function is also under investigation. Using a genetically modified strain of *E. coli* Nissle 1917 to produce NAPE-synthesizing enzymes, precursors to the NAE family of lipids, mice had lower food intake, insulin resistance, adiposity, and hepatosteatosis, with increases in hepatic NAE [364]. However, the effects on other bacterial members in the gut were not investigated.

To date, almost every type of known polyphenolic compound have been produced *de novo* or semi-*de novo* by genetically engineered strains of *E.coli* or *Saccharomyces cerevisiae* [365]. Modified strains have also been used to produce alkaloids (amino acid-derived compounds) [283, 366–370], polysaccharides [371], and various forms of terpenoids (e.g., lutein, lycopene, carotenes and carotenoids), a group of phytochemicals typically present in green foods and soy plants [372–376]. Recently, tryptophan-derived indolyguco-sinolate was produced in a strain of *S.cerevisae* after genome insertion with eight plant genes [377]. These remarkable progresses have also ensued development of novel or non-natural polyphenolic compounds [378, 379].

One of the drawbacks to genetically engineered therapies is the very real concern of biosafety and environmental contamination [351]. The fact is, when administering a live genetically modified organism, that organism is also released into the environment. Once released, there is a possibility of unintentional colonization of individuals, or food industries (e.g., dairy). Moreover, conditions in the human gastrointestinal tract favor natural horizontal gene transfer between bacterial members [380, 381]. Engineered bacterium should thus inherently include a biological containment system such as auxotrophy or other gene defect that necessitates supplementation with an essential metabolite or intact gene [382]. In addition, recombinant therapies designed on bacterial and probiotic strains

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currently listed by the U.S. Food and Drug Administration as generally regarded as safe (GRAS) should be subject to strict reevaluation protocols via regulatory frameworks [351].

To address the important issues of environmental safety, a modified strain of *Bacteriodes ovatus* (human commensal) was developed to deliver human transforming growth factor beta (TGF-$\beta_1$) but under the strict control dietary xylan (i.e. sole energy source) [353, 383, 384]. In a DSS model of colitis, xylan supplementation induced *B. ovatus* secretion of human TGF-$\beta_1$, as well as significantly improved DSS-induced colitis, in some cases superior to that of steroid treatment [384]. Additional studies investigating specific dietary compounds and functional capacity as a means of controlling therapy delivery and biosafety of genetically modified bacteria are highly warranted.

## Predicting probiotic-microbiota interactions in the host

In practice, a truly effective recombinant therapy would likely require long-term gastrointestinal colonization, and thus, should be capable of self-activation (or not) in response to specific environmental cues, over time in the host. This requires comprehensive understanding of the parameters governing competitive microbial colonization [385], preferred areas of local microbial colonization (i.e. small vs large bowel) [386], as well as how diet, environmental stimuli and mucosal immunity influence microbial ecosystems, or possible latent effects of stimulated immune pathways on microbiota composition. For instance, *Bacteroides* spp. appear to be resistant against antimicrobial peptides [387] and their abilities for colonization and resilience are largely determined by the presence of carbohydrates [388–390].

In order to predict the complex interactions between probiotic strains (natural or modified), mucosal immune systems, the gut microbiota (intestinal vs surface attached) [391–393] and host genetics, sophisticated *in vitro* systems, capable of dynamic, physiologically relevant environmental changes are essential [305, 394]. At present, various *in* and *ex vitro* models, testing inter-bacterial interactions have been applied, namely, single [395] and multi-stage chemostat models [394], synthetic 3-D tissue scaffolds with villous features [396], mouse ileal organoids [397] and a human gut-on-a-chip microdevice [218]. Assessment of recombinant therapies in gene circuits allows for detection of disease biomarkers and sometimes drug production, but are shown to result in high cellular burden and in turn, their condensed timeframes (i.e. 24 hours) may not adequately gage evolutionary stability of a recombinant therapy [305]. Stability of engineered therapies is a noted limitation as *in vitro* evolution experiments have shown bacteriophage functionality can reduce rapidly over time [398, 399]. Moving forward, efforts to enhance both robustness and long-term durability of engineered therapies and their testing models should help in the realization of an environmentally autonomous ‘intelligent’ engineered bio-organism as a NG-CAM strategy.

## Transformative therapy

Representing a somewhat more intrusive form of additive-type therapy, FMT focuses on changing intestinal microbiota communities as a whole. Procedures encompass infusion of fecal material sourced from a healthy donor, into the gut of an individual (i.e. the recipient) for the treatment of disease-specific dysbiosis, with the aim of restoring microbial balance.

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Fecal microbiota inoculum is delivered either to the upper gastrointestinal tract via nasogastric/nasojejunal tube or upper endoscopy, or to the lower intestinal area via enema or colonoscopy [400]. For treatment of recurrent *C.difficile* infections, FMT boasts 90% clinical success, proving twice as effective as antibiotic therapy alone [401]. Mechanisms as to exactly why FMT is effective are not fully understood, although abundance of butyrate-producing species *Lachnospiraceae* in donor microbiota was recently proposed [28, 402].

## FMT

Cumulative evidence seems to indicate that FMT-induced remission is possible in a subset of both UC and CD patients [403–405], although only two randomized controlled studies, bearing conflicting results, have evaluated FMT efficacy in UC patients, and no randomized controlled trial data is published for CD to date [347, 348, 403, 406]. In a 2014 meta-analysis of nine studies (included 79 UC and 39 CD patients), a remission rate of 36.2% in UC patients (pooled proportion) and 60.5% in CD patients (pooled estimate on subgroup analysis) was reported [406, 407]. These effects however, are not universal, nor are they sustained in either of the two IBD groups.

Failure of FMT in clinical studies may be attributed to various factors including, patient population (severe vs medically refractory), mechanism of action, stool donors, administration route and dosage, or other confounding factors such as smoking, diet and medication use [404, 406–409]. A recent study comparing lyophilized FMT product with fresh or frozen products (using same donors) revealed lyophilized product had slightly lower efficacy (vs fresh), whereas no difference between fresh and frozen fecal product was identified [410]. The hygiene hypothesis, one of the longest standing theoretical frameworks associated with the pathogenesis of IBD [4, 411–414], also happens to underpin the single most unexplored aspects of FMT administration, namely optimum timing for microbiota modulation. It is plausible that, remarkable efficacy may be observed if administered early in life, during certain key windows of plasticity in immune development. Equally, manipulation of microbial communities, perhaps early in diagnosis, could greatly improve long-term outcomes by attenuating disease progression.

One decidedly important issue concerning FMT therapy is the overall safety. The gut microbiome is a dynamic and living organism that constantly evolves over time, and a vast number of human-associated microbial and non-microbial (viruses, fungi) species remain undiscovered [415]. While short-term infectious risks of FMT appear to be definable and quantifiable, the theoretical risk of introducing pathogenic organisms that could later exacerbate disease conditions [407, 416], or the potential for unknown long-term consequences [408], are two caveats that continue to dampen enthusiasm in FMT clinical treatment. In an effort to mitigate these risks, several groups are currently investigating use of an ‘artificial’, synthetic stool mixture, designed to contain clinically active microbes [417, 418]. The stool substitute appears capable of curing antibiotic resistant *C.difficile* colitis [417] and should be pursued as a feasible alternative. Overall, the concept of FMT holds strong potential within the repertoire of CAM and NG-CAM for management of IBD. In the future, the most effective FMT modalities will like encompass defined microbial

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communities [419] infused into pre-characterized IBD recipients, pertaining to their gut microbiota community, diet, lifestyle and medication intake.

## Acknowledgments

Financial research support for this publication comes from the National Institute of Diabetes And Digestive And Kidney Diseases of the National Institutes of Health (NIH) under Award number P30DK097948 as part of the Digestive Diseases Research Core Centers program, as well as NIH awards DK091222, DK042191, DK055812, and DK097948 to FC.

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## KEY POINTS

The human gut microbiome exerts a major impact on human health and disease, and therapeutic gut microbiota modulation is now a well-advocated strategy in the management of many diseases, including inflammatory bowel disease (IBD).

Scientific and clinical evidence in support of complementary and alternative medicine (CAM), in targeting intestinal dysbiosis among patients with IBD, or other disorders, has increased dramatically over past years. The more recent scientific investigations have excelled through advancements in research technologies to allow redesign of many CAM strategies into that of precision, next-generation CAM (NG-CAM) systems, intended for the treatment of specific disease states.

Intriguing NG-CAM strategies, showing promise in IBD, include; 1) nutraceutical-producing bio-organisms, 2) genetically enhanced probiotic strains and usage of dietary compounds for controlling activation and biosafety, 3) microbiome-triggered encapsulation of bioavailable nutraceuticals (or drugs) for targeted, stepwise delivery, 4) ‘artificial’ stool for fecal material transplantation (FMT), and 5) bacteriophage delivery for precise elimination of specific microorganisms to reshape microbial populations. While the majority presently exist in their experimental and discovery phases, these envisioned NG-CAM strategies offer an intriguing prospect to the future management of IBD patients.

Delivery of ‘artificial’ stool replacements for FMT could provide an effective, safer alternative to that of human donor stool. Nevertheless, optimum timing of FMT administration in IBD remains unexplored, and future investigations to this end are essential.

As a prerequisite, future studies must consider host initial microbiome, as baseline composition of gut microbiota plays a key role in an individual responsiveness to nutrition modulation.

Animal and human studies continue to uncover the Pandora of interactions that endure between members of gut microbiome, their associated metabolites, dietary compounds, as well as the neurological and immune systems of the host, all of which characteristic to each individual. Exploitation of the communication bond between mind and microbe (i.e. mind-microbe balance) may prove to be a quintessential component for development of a truly effective therapeutic agent in IBD.

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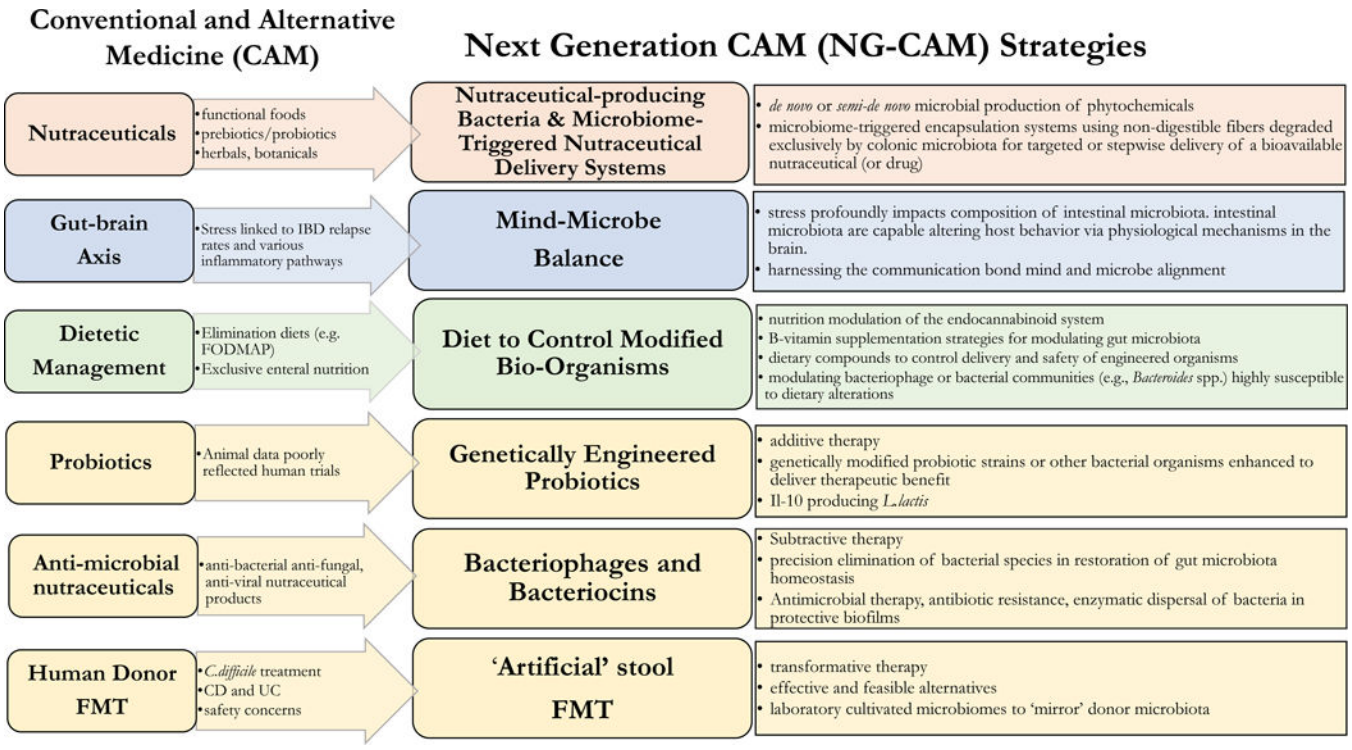


**Figure 1.**
Conventional and Alternative Medicine Strategies.