Complementary and Alternative Medicine Strategies for Therapeutic Gut Microbiota Modulation in Inflammatory Bowel Disease and their Next-Generation Approaches

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KEYWORDS

• Inflammatory bowel disease • Crohn disease • Ulcerative colitis • Gut microbiota • Complementary and alternative medicine • Nutraceuticals • Next-generation

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 the past years.
- Delivery of "artificial" stool replacements for fecal microbiota transplantation (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.

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- As a prerequisite, future studies must consider host initial microbiome, because 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 neurologic and immune systems of the host, all of which are characteristic to each individual.

INTRODUCTION

Crohn 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 the 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 toward 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 *Enterococcus*, *Streptococcus*, *Staphlococcus*, and *Propinibacterium*,[5] and possibly also via the placenta, introducing maternally derived microbes.[6] Further colonization, associated with infant delivery (ie, 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] ^{16}S-ribosomal RNA 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 more than 60 bacterial phyla exist in the world, the gut microbiome of a healthy human primarily consists of bacterial members belonging to 2 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 (eg, *Bifidobacterium* spp), Proteobacteria (eg, *Escherichia coli*), and Verrucomicrobacteria (eg, *Akkermansia muciniphilia*), with a possible smaller presence of Fusobacteria and Cyanobacteria.[13] Nonbacterial species, such as archaea, fungi (ie, mycobiota), and viruses (ie, virome), also inhabit the human intestinal tract,[14] with the human virome