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# Bifidobacterium and Mycosporin-like Amino Acid Cooperation: A New Era for Intestinal Diseases Treatment?

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## Abstract

Gastrointestinal microbiota includes bacteria, archaea, viruses, fungi and other eukaryotes. The genus *Bifidobacterium* is considered the dominant once, it has an important role on immunologic, hormonal and metabolic homeostasis of the host. Recent studies demonstrated that the Mycosporine-like Amino Acids (MAAs) had prebiotic effects and they modulated host immunity by regulating the proliferation and differentiation of intestinal epithelial cells, macrophage and lymphocytes. The safety of *Bifidobacterium* species is known; although they do not produce MAAs, their presence are required for immunological response continuity of intestine. Thereby we hypothesize that if we could create *Bifidobacteria* species producing MAAs *via* genetic engineering, they might have stronger immuno-stimulatory properties and might be used as more potent pharmacological agents in bowel diseases secondary to impaired microbiota.

**Keywords:** Mycosporine-like AminoAcids; *Bifidobacteria*; Genetic engineering

## Introduction

Microbial organisms live in close association with each other at human's body. The gut microbiota contains many different ecological community of commensal, symbiotic and pathogenic microorganisms [1,2]. The gut microbiota have anti inflammatory, antioxidant, antioncogenic effects and it contributes to the immunological, hormonal and metabolic homeostasis of the host [3,4]. Probiotics modify the environment of intestinal microbiota by making it unfavorable for pathogens; and produce antimicrobial peptides. As the gut microbiota becomes target of different diseases, the incorporation of probiotics to food products has been increasing, to assurance safety and healthy products [5]. Also different bioactive products acting topically in the gastrointestinal tract, and poorly absorbed had been studied in different diseases progress in order to modulate gut microbiota without systemic anti infective activity [6]. The genus *Bifidobacterium* belonging to *Actinobacteria* phylum and it consist of gram-positive, nonmotile, often branched anaerobic bacteria. The bifidobacteria are one of the major species of human colon microbiata and they are frequently used as probiotic agent [7,8]. Bifidobacterium species have immuno modulatory, metabolic and antiinflammatory effects which are not seen ın other gastrointesinal flora species [7,9]. *Bifidobacterium* species have the highest level of intrinsic hydrogenperoxide resistance causing antioxidant activity [10]. *Bifidobacterium's* oligosaccharide metabolism has been shown in many studies; it is separated from others by its fermentation ability [7,11]. Bifidobacteria use the fructose-6-phosphate phosphoketolase pathway to ferment carbohydrates;by this pathway indigestible fructans turn into Short Chain Fatty Acides (SCFA) as butyrate, which have beneficial effect on intestinal immunity and metabolism [12]. Bifidobacteria are the main source of butyric acid production and they are used as probiotic ingredient in many foods [13,14]. Recently diminished production of SCFAs are considered as the cause of antibiotic-associated diarrhoea, inflammatory bowel disease, pouchitis and other disfunctional intestinal disorders [15].

## Why Mycosporine-like Amino Acids?

MAAs are low molecular weight (<400 Da) amino acids. They have anampholyte nature and high denaturation temperature with water soluble properity [14]. MAAs act as UV-absorbers and photo-protectants [16-18]. They improve the growth of beneficial bacteria in the environment of harmful microbiota. MAAs are unique components of red seaweeds and seaweed components are known as supportive reinforcement of the microbiota in intestinal diseases [19-22]. MAAs had been shown to regulate intestinal epithelial cell differentiation and cytokine (IL-1β, IL-6) production [23,24]. Increased cytokine production, NF-κB activation induced a proliferative effect on epithelial intestinal cells and protect them in experimental colitis secondary to dextran sulfate sodium [24-28]. *Invivo* experiments showed anti-inflammatory effect of MAAs, indicating that they can reinforce membrane barrier function [29,30]. There are two biosynthesis pathways of MAAs. First MAAs biosynthesis pathway is the shikimate pathway [31] which is known as the synthesis way of aromatic amino acids. Second MAAs biosynthesis pathway is pentose phosphate pathway [32]. In both pathways, 4-deoxygadusol is the common precursor used to produce all MAAs. Transaldolase is an enzyme of the non-oxidative phase of the pentose phosphate pathway and Bifidobacterium strains have transaldolase enzyme. Confirmation of a biosynthetic gene cluster for MAAs from Gram-positive bacteria has been showed [33]. *Anabaena variabilist* PCC 7937 (*Cyanobacterium*) is able to synthesize MAAs [32]. Genome studies identified a combination of genes, YP_324358 (predicted DHQ synthase) and YP_324357 (O-methyltransferase),which were present only in *A. variabilis* PCC 7937 and missing in the other *cyanobacteria Anabaena sp. Anabaena* sp. PCC o7120 started to produce MAAs after genomic transfer (YP_324358 and YP_324357 genes) from *A. variabilis* PCC 7937 [34]. The *Bifidobacterium animalis subsp. lactis* KLDS 2.0603 strain was demonstrated to have the highest survival rate and adhesion ability in simulated gastrointestinal tract treatments [35]. The comparative genome analysis revealed that the KLDS 2.0603 has most

similar whole genome sequence compared with BB-12 strain. It seems that *cyanobacterium* is the source of MAAs and we hypothesize that the genes of cyanobacterium involved in MAAs biosynthesis could be transferred to *Bifidobacterium animalis* subsp. *Lactis* BB-12.

## Conclusion

There is no clinical data about bifidobacteria and biosynthesis of MAAs. Creating *bifidobacterium* species producing MAAs *via* genetic engineering could made better quality microbiota and more helpful to human health. MAAs produced *via* genetic engineering can be used not only as a probiotic, also as a pharmacological agent in inflammatory bowel diseases, irritabl bowel syndrome or chronic diarrhea. In our opinion, the production of this combination can open a gate of a new area for intestinal diseases treatment.

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