## Review Article

# Interaction between Gut Microbiota dysbiosis and Multiple Sclerosis

Shima Mehrabadi 1*

1. Department of Physiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.

*correspondence: **Shima Mehrabadi,** Department of Physiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran. Email: Sh-mehrabadi@razi.tums.ac.ir

**Abstract:**

Gut microbiota and also probiotics have a lot of interaction with immune system and can effect on immune homeostasis. Any changes in the level of gut microbiota or food probiotics can change immune system functions. Some recent studies indicated that disruption in level of the microbes can induce releasing of many pro-inflammatory factors and cause extensive inflammation in CNS. Unfortunately, the mechanisms of this process is not understood well and limited studies were done for detecting the relationship between gut microbiota and probiotics with neurological disorders associated with neuroinflammation. In this review, we gathered recent researches about this relationship to have a comprehensive look to effect of gut microbiota and diet probiotics in neuroinflammatory disorders and Multiple sclerosis as an important neuroinflammation disease.

**Keywords**: Gut microbiota, Multiple sclerosis, Neuroinflammation, Probiotic.



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## Introduction:

Recent studies indicated that the gut microbiota can influence on our brain and behavior (1, 2). Gut microbiota can impact on metabolic and neurological disorders. The microbiota play an important role in the health of body. It can help break down certain nutrients, which can be metabolized by host cells, and some of these products are involved in neural function(3). Also microbiota has a lot of communication with other organs and can affect the hemostasis and CNS directly or indirectly(4, 5). Microbiota can alter the level of our neurotransmitters and immune system functions by different pathways. Recent research has shown that intestinal microbiota have communication with the autonomic and central nervous system via different pathways including the ENS and vagal nerve(6, 7). Changes in our gut microbiota with change in our diet or consumption some medications like antibiotics or infections can alter this environment and change many homeostasis process(8, 9). So this findings show microbiota have crucial role in balance of our body hemostasis. The microbiota-gut-brain axis has an important role in many neuroinflammation disease(10, 11). Studies showed many neurodegenerative or autoimmune disease that associated with neuroinflammation are expanding in around of the world especially in developed country because of consumption of diets with many antibiotics and diets without any probiotics(12, 13). In recent decades, many research done in this area to find out how is it possible that microbiota dysbiosis induce neuroinflammation and can initiate many neurological disorder, but there are many mysterious pathways and interactions between gut microbiota, our diet with various probiotics and CNS. It has been clearly demonstrated that diet has a considerable effect on the composition of the gut microbiota. Different human populations can have vastly different intestinal microbiomes, and changes in diet lead to changes in microbiota composition. In this mini-review we want to discuss about recent findings showed that how changes in gut microbiota or treatment with probiotics can have a role in neuroinflammatory disorders inductions. A better understanding about this interaction may help us to find effective therapies or prevention for this type of diseases.

## How Microbiota promote neuroinflammation?

There are a lot of theory about relationship between alternation in microbiota and neuroinflammatory disorders. One of the possible theory is excessive immune system stimulation by changing the balance of microbiota may effect on intestinal permeability and induce systemic inflammation(14). When the integrity of these tight junction protein complexes diminishes there is an increase in intestinal permeability; the bacterial antigens can pass out of the intestinal lumen and travel to other locations in the body(15, 16). As a result, levels of antigens, like the endotoxin lipopolysaccharide, can increase in the blood circulation which could have systemic inflammatory effects (16-18). Also activation of enteric neurons system and enteric glial cells may contribute to the



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initiation of system inflammation in whole body and releasing many pro-inflammatory cytokines in blood stream that pass from blood brain barrier (BBB) and activate glial cell that result to neuroinflammation(19). So increased permeability of the gut and BBB may in many pathogenesis and other neurodegenerative disorders, especially those associated with aging. In addition, Gut microbiota can secrete many amyloids and lipopolysaccharides can trigger microglia by Toll like receptors (TLRs) and might contribute to the modulation of signaling pathways and the production of pro-inflammatory cytokines associated with the pathogenesis of many neurodegenerative disease like Alzheimer or Parkinson disease(20, 21). The other important theory is microbiota dysbiosis is can induce obesity and type 2 diabetes mellitus. It is now well accepted that obesity and diabetes mellitus is associated with chronic low-grade systemic inflammation(22). So this pro inflammatory cytokines in circulating system and free fatty acids reach the brain and initiate local inflammation, including microglial hyper-activation and proliferation and initiation of an inflammation cascade that may result loss of neurons and neurodegenerative disease(23-25). Also diabetes mellitus type -2 may induce amylin deposition in brain. Amylin deposition also trigger the microglia and could make extensive inflammation in CNS(23). Several other investigations indicated high fat diet also can cause hypothalamic inflammation (26, 27). The hypothalamus is responsible for many physiological functions like feeding and metabolism, reproduction, stress regulation, water balance, cardiovascular function(28). Many of these functions are related with attention, learning, memory and cognition. For this reason, neuroinflammation of the Hypothalamus, is associated with impaired cognitive function and can cause many neurodegenerative disease. So microbiota dysbiosis induce Diabetes mellitus-2 or obesity and this two situation can induce neuroinflammation from different ways. This local inflammations probably causes synaptic remodeling and neurodegeneration. Other theory that prove gut microbiota involved in neuroinflammation is the control of differentiation and function of immune system in peripheral systems and CNS by the gut microbiota(29, 30). Gut microbiota is required for normal immune system maturation and also they can influence the adaptive and innate immune systems in completely different ways(31, 32). Epithelial cells are central of the immune system of the gut. Microbiota can elicit innate and adaptive immune systems and cooperate to protect the host and maintain intestinal homeostasis from different ways(32). They can also enroll leukocytes to complement their barrier function or to participate in the activation of gut adaptive immune responses. If microbiota dysbiosis happens, the regulation of immune system hemostasis disrupted and may release many proinflammatory cytokines by immune system lead to many auto-immune and also many neuroinflammation disease(1, 33). As a result recent data indicate that microbiota have important role for mammalian bodies in having a healthy brain and protect us from many neuroinflammatory disorders.

## Gut microbiota components change in Multiple Sclerosis:



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Multiple sclerosis (MS) is a chronic autoimmune and pro-inflammatory demyelinating disease that effects on the central nervous system. The etiology of MS is not fully understand, but there are strong evidences to both genetic and environmental factors are involved in MS development (34). It is hypothesized that there is a bi-directional relationship between the gut microbiota and MS(35, 36). Intestinal microbiota dysbiosis observed in autoimmune diseases like MS and associated with decreased microbiota function and diversity, impaired gut barrier function, increased inflammation and decreased T regulatory cells functions in the gut(37). Many environmental factors such as obesity or vitamin D levels known as risk factors for MS also influence the gut microbiota which modulates the immune system(36, 38). Studies showed that the regimes with less probiotics could be an important environmental factors that arise MS in population. It can be an explanation for the geographical differences seen in MS incidence it can be from differences between gut microbiota components that result from different food regimes in around of the world. Also gut microbiota from patients with MS were shown that some components of the microbiota activate a pathogenic inflammatory response(39).Studies showed that the composition of the gut microbiota alter in MS and this alternation has important role in pathology and progression of MS(36). For example absence of Fusobacteria was associated with over three times the hazard of an earlier relapse(40). In another study the use of probiotic capsule for 12 weeks among patients with MS had treatment effects on parameters of mental health, inflammatory factors, markers of insulin resistance, HDL and MDA levels (41). Probiotic supplement decreased the levels of IL-6, and increased concentration of NO and IL-10 in serum of MS patients(42). Improvement of clinical scores by probiotic bacteria is contributed to alteration of immune responses by inhibition of inflammatory cytokine and increased anti-inflammatory cytokine and T regulatory. It seems that the probiotic treatment may improve clinical symptoms by a balance in inflammatory and anti-inflammatory responses in MS patients. Further, decreased oxidative stressors might be involved in controlling the clinical symptoms in the patients with MS(43). Gut microbiota affects both local immune responses and immune responses in the peripheral, it could be associated with different treatment effectiveness among patient. Also studies showed that Pretreatment with probiotics before MS induction significantly suppressed MS and demyelination development and delayed disease onset (44). Also it seems that there is an association between gut microbiota profiles MS and subsequent relapse risk (45, 46). These findings suggest that manipulation of the gut microbiota by the use of probiotics, can be beneficial for MS patients. Another recent studies discovered probiotic with immunoregulatory properties also has the potential to become a new therapeutic treatment for autoimmune disease.

## Conclusion:



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In fact, gut microbiota have an important contribution role in regulation of immune system and in host body. Also they have a crucial role for preventing neuroinflammatory disorder in the CNS. MS is a complex disease with a vast neuroinflammation and with a large variety of associated environmental risk factors. In fact, combined therapies should be used to impact not only the gut microbiota but also other MS-related environmental risk factors.

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