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Effects of Probiotics, Prebiotics and Synbiotic Supplementation on Cognitive Impairment: A Review

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ABSTRACT

Learning and memory formation are the two essential terms widely used in the field of cognition. Learning can be defined as acquiring new information or skills. Memory is formed due to changes in the neuronal system as a result of continuous stimulus exposure. Both learning and memory are fundamental processes that occur in all living organisms. Memory is broadly categorized into two different categories such as short-term memory (STM) and long-term memory (LTM). Compared to STM, LTM plays an essential role in the day-to-day activities of different living organisms. LTM requires RNA and protein synthesis-dependent mechanisms for memory storage, which lasts up to their lifetime. LTM formation is initiated when the neurotransmitters are released from the presynaptic neuron; further released neurotransmitters bind with their respective receptors present in the postsynaptic neuron and initiate the calcium influx. Calcium influx results in the further activation of molecules involved in the neuronal signaling pathway and results in memory formation. Present review reports the outcome of recent studies which showed that probiotic supplement is responsible for the retrieval of memory in case of memory impairment and its uses in the treatment of neurodegenerative disorders like mild cognitive impairment (MCI), Alzheimer's disease (AD). Recent research studies were shown that probiotic microorganisms may positively regulate neurotransmitter release and increase the calcium influx, brain derived neurotrophic factor (BDNF), and N-methyl-D-aspartate receptor (NMDAR) and plays a pivotal role in the LTM formation in gut-dysbiosed & memory-impaired animal models.

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1 Introduction

Synaptic plasticity refers to the activity-dependent changes that occur in synapses and plays a prominent role in memory formation (Kind and Neumann 2000; Sweatt 2001; Abraham et al. 2019). Several experimental animal models were shown that changes in the synaptic strength are occurred due to repeated stimulus exposure/activity. These changes are referred to as long-term potentiation (LTP) (Malenka et al. 1992; Thiels and Klann 2001; Abraham et al. 2019; Evans et al. 2021). LTP was first identified by terjeløмoin the year 1966. After the discovery of LTP, several studies have been attempted to focus on the change of locus, pre/postsynaptic currents. Recently, it is accepted that postsynaptic signaling mechanisms are most needed for the LTP induction and serve as a primary mechanism to maintain increased synaptic response (Waltereit et al. 2001; Yuste and Bonhoeffer 2001; Evans et al. 2021).

At the initial phase of memory processing in the brain, memory formation may be inhibited by various hindrances like seizures, trauma, inactivation of neuronal pathways, brain lesions, and inactivation of specific transcription factors, translation, or specific blockade of molecular pathways. During the initial memory processing, memory impairment happened due to various reasons such as trauma, seizures, neuronal pathways inactivation/blockade, of inhibition of neuronal transcription factors. Thereby transcription plays an essential role in memory consolidation or its retainment. Long-term plasticity changes result in long-term facilitation (LTF), LTP, and long-term depression (LTD) which requires both transcription and protein synthesis (Baker-Herman and Mitchell 2002; Roberts and Glanzman 2003; Evans et al. 2021; Lin et al. 2021). Several animal studies have been shown that long-term memory (LTM) needed *de novo* protein synthesis during the first few hours of training (Schafe and LeDoux 2000; Scharf et al. 2002; Igaz et al. 2006; Abraham and Williams 2007; Lin et al. 2021; Evans et al. 2021).

The learning process is associated with activity-dependent changes and results in neurotransmitters' release (Lovinger 2010; Bai and Suzuki 2020). Neurotransmitter release results in the activation of neuronal signaling pathway with the help of several proteins like protein kinase A (PKA), extracellular signal-regulated kinase-1/2 (ERK-1/2), mitogen-activated protein kinase (MAPK), and cyclic AMP response element-binding protein-1 (CREB-1) (Yoon and Seger 2006; Ganesh et al. 2010; Ganesh et al. 2012; Mukilan et al. 2015; García-Pardo et al. 2016; Mukilan et al. 2018a, 2018b). Activation of ERK-1/2 results in the phosphorylation of CREB-1 (Peng et al. 2010). Further, phosphorylated CREB-1 results in the activation of the immediate early gene (IEG) cascade and other postsynaptic density protein (PSD), which results in the formation of LTM (Ganesh et al. 2010; Ganesh et al. 2012; Mukilan et al. 2015; Mukilan et al. 2018a, 2018b).

In normal healthy persons, gut microbiota was needed for the proper functioning of the central nervous system (CNS) through endocrine, neural, and immune pathways (Grenham et al. 2011; Moloney et al. 2014; Ma et al. 2019). Pathogenic infection or stress exposure stimulates the secretion of corticotrophin-releasing factors (CRF) via the hypothalamus-pituitary-adrenal axis from the brain. CRF disturbs the gut microbiota and increases the production of endotoxins (Bailey and Coe1999; Mayer et al. 2015; Misak et al. 2020). These endotoxins limit the secretion of serotonin and catecholamines (Linthorst and Reul 1998; Fung et al. 2017; Yang and Chiu 2017). Serotonin and catecholamines increase interaction between the gut microbiota and CNS. By this signaling pathway, CNS maintains homeostasis. Impairment or dysregulation of this signaling pathway resulted in autism, Alzheimer's disease, memory impairment, and neurodegenerative disorders (Linthorst and Reul 1998; Fung et al. 2017; Salami 2021). Recent studies were shown that treatment with probiotic microorganisms was used to overcome the impaired cognitive decline in autism and Alzheimer's disease (Petrof et al. 2013; Choi and Choi 2016; Asl et al. 2019; Morshedi et al. 2020).

Probiotics are beneficial living microorganisms, when it was taken in an appropriate dose it supports the host in many ways like the improvement of cognition, immune system, and also it will supply needed antioxidants (FAO/WHO 2002; Sherman et al. 2009; Kwok et al. 2014). Compared to probiotics, prebiotics was formed by the fermentation of non-digestible ingredients by the beneficial gut microbiota. These prebiotics enhance the growth and activity of beneficial gut microorganisms. The formed probiotic/prebiotic precursor molecules increase the growth and metabolic activity of beneficial microorganisms present in the gut. Thereby it increased the short-chain fatty acid (SCFA) level and also modifies alpha-synuclein protein (Franco-Robles and López 2015; Markowiak-Kopeć and Ślizewska 2020). SCFA were used for the regulation of neurotransmitter release and have a direct effect on the expression level of brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF). It will also be shown that SCFA act as an essential molecule for the signaling between the gut microbiota and brain (Montarolo et al. 1986; Dale et al. 1987; Gräff and Tsai 2013; Buffington et al. 2014; Franco-Robles and López 2015; Heyck and Ibarra 2019; Markowiak-Kopeć and Ślizewska 2020).

Recent research reports have shown that the gut microbiota plays an important role in the regulation of gut-brain axis (Wong et al. 2018; Misak et al. 2020). Some gut bacterial strains may also regulate the level of neurotransmitters like γ-aminobutyric acid (GABA)(Wong et al. 2003). Recent studies have shown that various neurotransmitter levels were regulated by some bacterial strains present in the gut. Regulated neurotransmitters may include γ-aminobutyric acid (GABA) (Wong et al. 2003; O'Donnell et al. 2020), serotonin (5-HT), dopamine (DA), and noradrenaline (NA)

(Chen et al. 2017). These neurotransmitters potentially regulate calcium influx and other molecules involved in the formation of LTM (Romo-Araiza et al. 2018; Rezaeiasl et al. 2019; Yang et al. 2020). Present review article trying to explore the role of prebiotics and probiotics in the formation of LTM and its uses in the treatment of memory impairment in neurogenerative disorders like Alzheimer's disease (AD), epilepsy, Parkinson's disease (PD), autism spectrum disorders (ASD).

2 Effect of neuro inflammation on memory impairment

Degeneration of neurons/neuroinflammation within the CNS are associated with the decline in memory formation (Romo-Araiza et al. 2018). Mild cognitive impairment (MCI) is regarded as the intermittent stage of memory decline between healthy apoptosis and dementia (Tajiri et al. 2017; Romo-Araiza et al. 2018; Tobin et al. 2019). MCI results in the loss of neurons in different brain regions like the hippocampus. Loss of neurons may also be related to the defects of mitochondria and oxidative stress. Oxidative stress results in increased levels of proinflammatory cytokines, which results in neuroinflammation. In later stages, there is a probability of conversion of MCI to Alzheimer's disease (Baierle et al. 2015; Zhao et al. 2015; Romo-Araiza et al. 2018; Tobin et al. 2019).

Neuroinflammation is generally associated with cognitive memory decline. This neuroinflammation results in the inflammation of the hippocampal tissue region. Hippocampal tissue inflammation will result in decreased plasticity changes, which results in impaired LTM formation (Di Filippo et al. 2013; Zhao et al. 2019). Decreased plasticity changes result in the low-level synthesis of glutamate and downregulation of N-methyl-D-asparate receptor (NMDAR) in the hippocampus's CA1 and CA3 region (Kumar and Mehta 2011; Bye and McDonald 2019).The downregulation of NMDAR results in impaired LTM formation (Rosi et al. 2005; Di Filippo et al. 2013; Baierle et al. 2015). Other than NMDAR, Brain-Derived Neurotrophic Factor (BDNF) is also down-regulated during neuroinflammation/gut dysbiosis which results in impaired memory formation (Ryan and Nolan 2016; Mora 2013).

3 Role of short-chain fatty acid (SCFA) on memory enhancement

Intestinal probiotic microorganisms are needed for short-chain fatty acid (SCFA) production. This SCFA are made up of carboxylic acids, these carboxylic acid are present with the aliphatic tails of 1-6 carbon. In these 6 carbon molecules, 3 carbon molecules {acetate (C2), propionate (C3), and butyrate (C4)} were

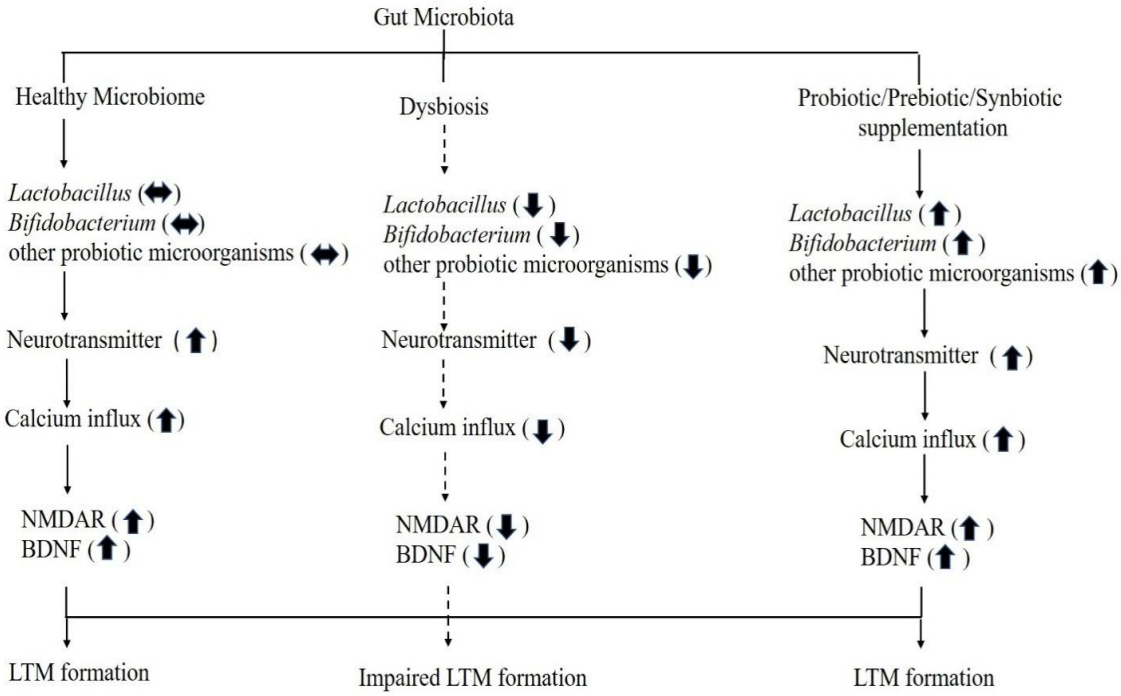

Figure 1 Effect of gut microbiota in the long-term memory (LTM) formation. A) Gut microbiota plays a main role in the development of LTM by the release of neurotransmitters (ex. serotonin) in its normal state and further results in the increase of calcium influx and brain derived neurotrophic factor (BDNF) and N-methyl-D-aspartate receptor (NMDAR). B) dysbiosis affects the normal level of gut microbiota, low level of gut microbiota inhibits the neurotransmitter release, decrease the calcium influx and downregulates BDNF &NMDAR.Low levels of BDNF & NMDAR results in the impaired LTM formation C) Treatment with probiotics restores the normal gut microbiota and restores the LTM memory formation.

produced by anaerobic fermentation of dietary fibers (DF) by the intestinal microorganisms. In these aliphatic tails, three different carbon molecules will be synthesized from the dietary fibers with the help of gut microbiota by anaerobic digestion. Some of the carbon molecules were produced by the Acetate are the most abundant SCFA produced in the gut. Acetate was made from acetyl-CoA from glycolysis (den Besten et al. 2013; Duncan et al. 2002). Propionate and butyrate formation occurs from the carbohydrate metabolism of glycolysis (Louis and Flint 2017). Levels of SCFA decline with age and microbial imbalance. Microbial imbalance results in the increase of pathogenic bacteria Proteobacterium and results in the brain's inflammation (Caracciolo et al. 2014; Romo-Araiza et al. 2018)

Brüssow stated that both probiotics and prebiotics were used for the production of SCFA, increasing neurotrophic factors and neuronal plasticity. Agave inulin a most commonly used prebiotic stimulates the growth of *Enterococcus faecium* (probiotic bacterium), thereby indirectly promoting butyrate synthesis (Huang et al. 2017). Among the three SCFA, butyrate functions as a histone deacetylase inhibitor, enhancing the upregulation of BDNF expression in the different regions of the brain and inhibiting the secretion of proinflammatory cytokines (Park et al. 2016; Kim et al. 2014). Recent research findings were shown that healthy gut microbiota increases butyrate production; the presence of enough butyrate level reduces neuroinflammation and increases BDNF, NMDAR levels in the specific brain region, and upregulation of BDNF, NMDAR results in increased synaptic plasticity (Stilling et al. 2016; Pineda-Rodriguez et al. 2017; Canani et al. 2018).

4 Effect of probiotics on long term memory formation

Several intestinal microbial species influence the physiology, development, and maintenance of an individual's health in the form of gut microbiota. Gut microbiota can be differentiated into three major categories viz., bacteria, viruses, and fungi. These microorganisms regulate intestinal pH and act as a preventive barrier against infectious agents. A healthy level/ equilibrium of intestinal microbiota plays an important role in the maintenance of proper health. A healthy state shows the mutual relationship between gut microbiota and the nervous system (Jiang et al. 2017). Equilibrium of intestinal microbiota was mainly affected by different lifestyles like diet (Gentile and Weir 2018), alcohol consumption (Hillemacher et al. 2018), smoking (Savin et al. 2018), and changes in circadian rhythm (Kaczmarek et al. 2017). However, alteration in the gut microbiota may induce changes in brain activity and also cause neurological disorders like AD (Angelucci et al. 2019). Affected intestinal microbiota equilibrium comes back to normal by consuming probiotics/prebiotics/ synbiotic supplementation (Kaczmarek et al. 2017; Gentile and Weir 2018; Hillemacher et al. 2018; Savin et al. 2018; Hadizadeh et al. 2019).

Probiotics produce beneficial effects on the host's health (Mukherjee et al. 2018). Most bacteria are used as probiotics; probiotic bacteria are needed to synthesize substances required for a host. The presence of a sustainable number of necessary substances prevents inflammation and related diseases (Mukherjee et al. 2018). The most commonly used probiotic strains include *Lactobacillus* and *Bifidobacteria*. Both of these strains are present in yogurt, fermented cheese, and vegetables. Other than probiotics, we also consumed dietary fibers; anaerobic fermentation of dietary fibres results in the formation of SCFA (Daliri et al. 2018; Mukherjee et al. 2018). This type of probiotic microorganisms may synthesize and release different neurotransmitters like serotonin, GABA, histamine, and dopamine (Gareau 2014; Dinan and Cryan 2017). Several gut microorganisms are responsible for the synthesis of neurotransmitters like dopamine, noradrenaline, serotonin, GABA, acetylcholine, and histamine which plays a main role in long-term memory formation (Stanaszek et al. 1977; Tsavkelova et al. 2000; Landete et al. 2007; Shishov et al. 2009; Özoğul et al. 2012; Pokusaeva et al. 2017). However, gut microbiota imbalances play an important role in the deficient synthesis of biogenic amines and neurotransmitters which will have a direct impact on long-term memory formation (Matsumoto et al. 2013). Prebiotic or probiotic treatment increases neurotransmitter level and improves the cognitive functions in memory-impaired animal models (Lyte 2011; Barrett 2012; Dinan 2015; Sarkar et al. 2016; Bermúdez-Humarán et al. 2019).

Neurotransmitters produced by the probiotic microorganisms at first cross the blood-brain barrier and reach the central nervous system (CNS) (Pokusaeva et al. 2017). Among the pool of neurotransmitters, serotonin (5-HT) is synthesized from the amino acid tryptophan. At first, amino acid tryptophan is converted to 5-hydroxytrptophan (5-HTP) with the help of tryptophan hydroxylase. Formed 5-HTP is again reconverted to 5-HT by the aromatic amino acid decarboxylase (AACD) (Adell et al. 2002). This 5-HT is first reported to be involved in learning and memory formation by the 1980s (Altman and Normile 1988). This 5-HT is having multiple neural markers like receptors and transporters (McCorvy and Roth 2015). Further, 5-HT is synthesized from serotonin synthesizing neurons. Serotonin synthesizing neurons are present along the brainstem's midline; the most prominently present in raphe nuclei. Axons of these serotonin synthesizing neurons innervate almost all regions of the brain. Activation of 5-HT receptors stimulates adenyl cyclase (AC), this AC induces the rapid increase of cyclic adenosine monophosphate (cAMP) levels which directly stimulates protein kinase A (PKA) activity. Further, PKA increases MAPK/ERK kinase (Mohamed et al. 2005). ERK 1/2 cascade activation is necessary to consolidate the learning

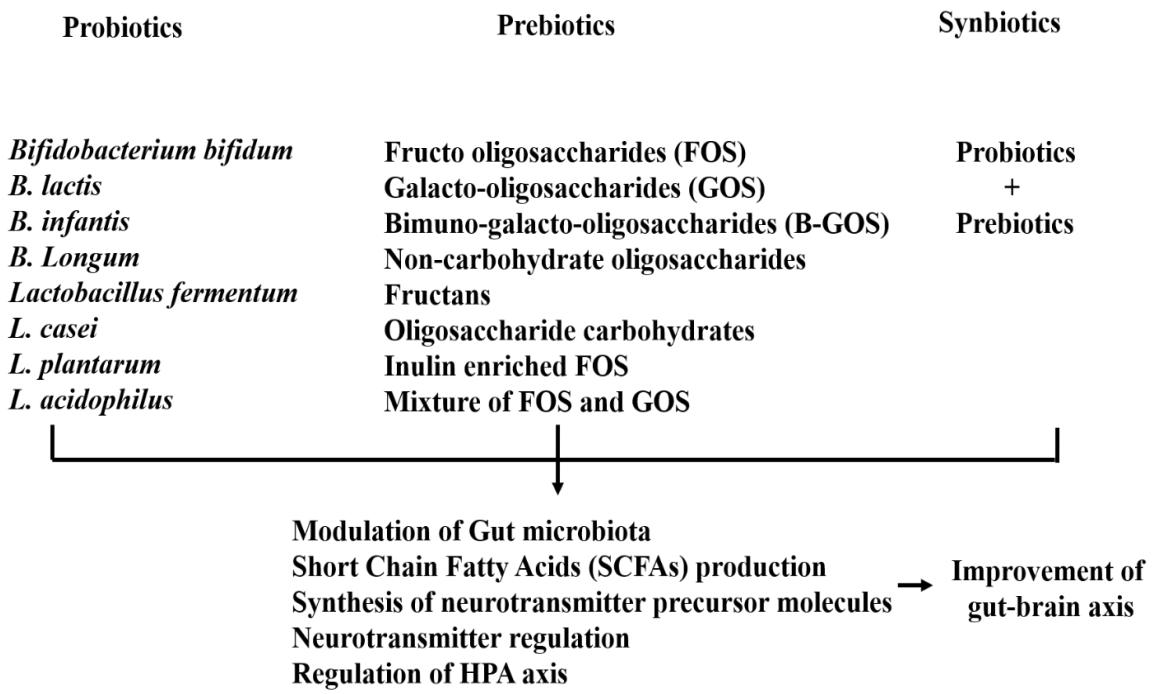

Figure 2 Role of probiotics/prebiotics/synbiotics on the improvement of gut-brain axis

paradigm (Ganesh et al. 2010; Ganesh et al. 2012; Mukilan et al. 2015; Mukilan et al. 2018a; Mukilan et al. 2018b). Compared to the ERK cascade, BDNF is also involved in long-term memory formation. BDNF is needed for stimulating hippocampal-neocortical interaction during the consolidation of memory (Bambah-Mukku et al. 2014). During the consolidation of long-term memory, hippocampal-neocortical interactions were stimulated by the BDNF (Bambah-Mukku et al. 2014; Miranda et al. 2019).

5 Effect of prebiotic and synbiotic supplementation on memory formation

Recent studies were evidenced that early life intake of prebiotic is associated with improvement of cognitive abilities, LTM formation in the early and middle stages of life. During early life, gut microbial colonization is needed for the development of the neuronal structure and its function (Williams et al. 2016). Treatment of neonatal rats with a galacto-oligosaccharide prebiotic (BGOS) increases the expression of N-methyl-D-asparate receptor (NMDAR) subunit-GluN2A, synaptic proteins, and brain-derived-neurotrophic factor (BDNF) in the hippocampal brain region and also alters the neurotransmission during memory impairment. Other than BGOS, oral administration of 2'-fucosyllactose (2'-FL) also showed a higher level of long-term potentiation (LTP) (Williams et al. 2016; Oliveros et al. 2016). Other than prebiotic, synbiotic (probiotic and prebiotic) supplementation is also used for the development of memory in memory-impaired animal models. Romo-Araiza et al. (2018) stated the effect of probiotic and prebiotic supplementation on spatial memory formation.

6 Impact of probiotic supplementation on neural dysfunctions

Recent research findings showed that probiotic supplementation plays an essential role in the prevention of neural dysfunctions by regulating age-related cognitive impairment. Song et al. (2013) tested the effect of prebiotic galactooligosaccharides (GOS) on the neuroprotective effect in amyotrophic lateral sclerosis (ALS). The outcome of the study showed that the administration of GOS reduced motor neuron loss, improved the consequences of atrophy, and also stated the role of probiotic yogurt in the disease onset improvement. Other than GOS, probiotic yogurt administration also delayed disease onset and increased the lifespan of treated mice. Yang et al. (2020) investigated the effect of probiotics on the deficits of intestinal gut microbiota and restores cognitive function using the probiotic preparation of *Bifidobacterium lactis*, *B. bifidum*, *Lactobacillus casei*, and *L. acidophilus* (ProBiotic-4) on SAMP8 (Senescence-accelerated mouse prone 8) mice. Oral administration of ProBiotic-4 for 4, 8, and 12 weeks significantly improves the deficits of the microbiota-gut-brain axis and cognitive function (Yang et al. 2020).

Conclusion

Recent studies were shown that probiotic, prebiotic, and synbiotic supplementation is used as a clinical tool to treat memory decline

in AD, mild cognitive impairment (MCI), and type 2 diabetes mellitus (T2DM) induced memory impairment. The most commonly anti-inflammatory property of the synbiotic supplementation is used for the treatment of neurological disorders and cognition decline in MCI. Compared to MCI, T2DM is a common metabolic disease that leads to memory dysfunction in the brain and is also associated with complications of gut-brain disorders. Some of the important research findings were shown the impact of probiotic, prebiotic, and symbiotic supplementation on the improvement of cognitive complications and plays the main role in the strengthening of neurotransmitter concentration (especially serotonin), BDNF/TrkB/CREB signaling pathways in different brain regions. Strengthening of this neuronal signaling pathway results in the improvement of memory during cognitive decline. Along with this supplementation, SCFAs will also play a positive role on the brain-gut axis. These SCFAs may also be produced by anaerobic fermentation of non-digestible ingredients with the help of certain probiotic microorganisms. The newly formed SCFAs are also involved in the new protein synthesis, enhance histone acetylation and do long-term plasticity changes in the brain. The long-term plasticity changes were enhanced by histone acetylation and could be improved with the help of HDAC inhibitors (HDACi). These SCFAs also act against neuroinflammation and inhibits the expression of proinflammatory cytokines in the presence of butyrate and sodium butyrate. Simply, SCFA increases the levels of BDNF, NMDAR through the supplementation of pre and probiotics along with food. Thereby SCFA plays an essential role in reducing the risk of Alzheimer's disease development due to aging and brain injuries. Other than synbiotic and SCFAs, ProBiotic-4 is also used to treat gut microbiota dysbiosis, which will result in the improvement of cognitive function. However considering the data reviewed here, shown that probiotic, prebiotic, and synbiotic supplementation intake reduces cognitive impairment, memory decline and restores synaptic plasticity and specific gut microbiota changes occur due to lead-led memory impairment, MCI, AD, and neurodegenerative disorders. Other than the restoration of gut microbiota, these supplementations are also used for the restoration of memory impairment and morphological abnormalities of dendritic spines. Thereby present review focused on the effect of probiotic, prebiotic, and synbiotic supplementation on the treatment of memory impairment caused due to aging, MCI, and the role gut-brain axis in the long-term memory formation. This review elaborates the role of gut microbiota on the synthesis of the neurotransmitter, activation of neuronal molecules in long-term memory formation.

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Ethical approval

This article does not contain any studies with human participants or animals performed by the author.

Conflicts of Interest

The author declare no conflict of interest.

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