Chapter

Probiotics in Health and Immunity: A First Step toward Understanding the Importance of Microbiota System in Translational Medicine

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Abstract

There are mounting evidences showing the relation of chronic inflammatory and autoimmune diseases with the uncontrolled intensification of gut dysbiosis. This position asserts that an elevated presence of pathogens and bacterial, fungal, and viral components is directly involved in inflammatory metabolic diseases with a strong alteration of autoimmune components such as in inflammatory bowel syndrome (IBS), ulcerative colitis, and Crohn's disease. Furthermore, the increase of unbalanced enteric microbiota is also connected to other types of conditions of metabolic origin such as diabetes mellitus, atherosclerosis, and osteo-degenerative conditions. As a matter of fact, evidence confirmed that gut damages histologically inspected revealed a situation with high expression of pro-inflammatory cytotumor necrosis factor-alpha (TNF-α), and IL1β, IL-2, IL-4, IL-6, and IL-17 together with high level of mucin-2. This chapter focuses on diverse topics related to microbiota dysfunction and systemic health condition and regenerative capacity and the therapeutic role of probiotics in gut health and disease emphasizing the potential beneficial role of probiotics in idiopathic inflammatory metabolic diseases. In brief, outcomes demonstrate that an intimate relationship between microbiota, metabolism, tissue/cellular damages, and regeneration is standing. Within this scenario, the gut certainly plays a big part of the regenerative mechanisms in translational medicine.

Keywords: inflammatory bowel syndrome, ulcerative colitis, Crohn's disease, gut dysbiosis, short-chain fatty acids, central nervous system, experimental autoimmune encephalopathy, vagus nerve, tumor necrosis factor-alpha, IL1β, IL-2, IL-4, IL-6, IL-17, mucin-2, probiotics

1. Introduction

The oral-gastro-intestinal-sex-skin can be classified as unique large and heterogeneous apparatus populated by a huge variety of microorganisms, bacteria, virus, fungi, and other single-celled creatures, that compose the totality of human microbiota that contributes together with bone/skeleton system, to maintain the body energy homeostasis. The human body hosts something like 10–100 trillion microbial cells that coexist in a strict fruitful symbiotic relationship that persists as long as the body is kept in a balanced healthy state [1, 2]. The gut plays an important role in regulating metabolic immune activities. The gut's essential task is the absorption of nutrients and the synthesis of important micromolecules obtained from food that cannot be assimilated by the stomach and small intestine [1–3]. Xyloglucans and fructo-oligosaccharides from vegetables and fruits, protein, and lipids; the assimilation of essential vitamins like vitamins B-12, D, and K; and the synthesis of hormones like serotonin from tryptophan amino acid take place right in the gut, thanks to the constant activity of its entire microbiota. The microbiota are able to produce 50–100 mmol·L—1 per day of extremely important short-chain fatty acids (SCFAs), such as acetic, propionic, and butyric acids—and serve as an energy source to the host intestinal epithelium and skeleton [1–4].

The importance of SCFAs has been well described by several studies during the last decade; the activity of acetic acid, for instance, has been found to be essential against infections, in blood pressure regulation and against sclerotic plaque deposition in arterial walls. The presence of butyric acid is an essential anti-IBS agent due to its immune-modulator properties and anti-inflammatory action, while propionic acid has been found to be important in preventing obesity and diabetes 2 [1–4].

Although bacteria, viruses, and fungi might be very harmful and dangerous, they are indispensable for life as well. This symbiotic coexistence throughout the millennia made a deep crucial biological impact on human species, and it has become essential not only for survival but for evolution as well. Accumulating evidences have clearly demonstrated how part of these specific microorganisms can resume specific immunomodulatory roles and the way they affect either composition function or migration of various immune cell subpopulations from one site to a different location. For instance, oral macrophages may migrate under the influence of specific signal induction of local microbiota from oral either to the lungs or even the brain passing through the blood brain barrier (BBB) [5–10].

The outcomes from experiments performed on germ-free (GF) mice confirmed the great role of gut microbiota in the upsurge of immune system deficiencies. GF animals were shown to have compromised Paneth cells and low levels of natural killer (NK) cells, dendritic cells (DCs), and α/β + and γ/δ + T cell populations that play an important role in defense and pathogenesis during inflammation and infection, especially against certain types of malignancies. In addition, GF animals were highly susceptible to frequent infections due to a decline in angiogenin-4 (Ang4), a powerful antimicrobial part of the class of microbicide proteins in Paneth cells [5–10].

The alteration of the gut microbiota may contribute to open up the invasion of exogenous pathogens that may destabilize the whole intestinal mucosa. The pathogen systematic overgrowth will trigger a cascade of strong inflammatory responses making intestinal mucosa highly susceptible and motile. The chronic inflammation will weaken the endothelial tide junction to the point that the walls become highly relaxed and permeable causing the phenomenon known as "leaky gut" that allows

the free, uncontrolled passage of microorganism into the system via the bloodstream and tissues where they start allocating. In fact, the presence of these typical gut residents could be found in eroded, inflamed, and degenerated joints and organs such as the lungs, heart, brain, and liver [11–13].

2. Gut dysbiosis: a modality to understand neurodegenerative diseases: the disruption of blood-brain barrier (BBB) may explain the gut-oral-brain axis relationship

The high and uncontrolled levels of pathogenic microorganism colonizing the gut contribute to a condition known as dysbiosis [14]. Since few years the dysbiosis has been associated with a variety of degenerative patterns that tend to subvert the metabolic/neuro/hormonal/immune axis contributing to a variety of disorders that round to different body systems ranging from skeleton, cardiovascular, to neuro system. There are several mechanisms proposed that are able to trigger this state of systemic disorders; one of the possibilities is linked to bacterial metabolites and immune-modulating mediators that contribute to the high permeability of intestinal mucosa allowing local pathogens to get through the mucosal barriers triggering a huge variety of immune responses. A second and though related mechanism is the sabotage of SCFAs' production; the consequences of this mechanism are the abrupt breakdown of energy balance mechanism, a reduction of cell-bacteria signaling pathway, and the worsening of epithelial cell layer integrity due to the decreased production of tight junction proteins which allows the translocation of LPS into the submucosa as well. The significant presence of pro-inflammatory cytokines and interleukins such as TNFα, IFN-γ, IL-1β, IL-2, IL-4, IL-5, and IL-6 is the peculiar trait of a dysbiotic gut (**Figure 1**) [14–16]. A third way of dysbiosis transmission is through the vagus nerve (VN), the main component of parasympathetic nervous system (PSN) which also constitutes an effective bridge of the gut/CNS axis. This hypothesis, today supported by a concrete line of evidences, proposes the existence of a reciprocal interference way between the CNS and gut through the VN. In this view the VN is able to perceive microbiota movement, grade of activity, and therefore degradation; on the other hand, pathogens once out from the gut mucosa barrier are able to communicate and move to the CNS through the VN pathway [14–18].

These essential structural alterations are at the base of neurodegenerative pathologies. Though it is a unique pathological aspect, we may see the presence of a common configuration indeed, which is a shared neurological chronic inflammatory pattern. In all these cases, the chronic neuro-inflammatory condition is characterized by an abnormal hyperactive behavior of neural immune cells, the microglia, known as macrophages of the brain [18, 19]. The chronic inflammatory state that from the gut opens up the pathway of pathogenic microbiota invasion all the way through oral and brain compartment, which is the hallmark of neurodegenerative disorders' dynamic pathogenesis. Patients with Parkinson's disease (PD), Alzheimer's (AD), multiple sclerosis (MS), or amyotrophic lateral sclerosis all present a variety of disturbances in intestinal microbial compared to healthy individuals. Neurodegenerative-affected patients' intestinal and fecal analysis showed a clear clinical picture of microbiota dysbiosis. The test outcomes showed high level of coliform and gram-negative bacteria from *Ralstonia* genus concomitantly with low critical level of anti-inflammatory strains related to *Blautia*, *Coprococcus*, and *Roseburia* genera. Another indicator was also noted; it was the low presence of *Prevotella* generally seen as beneficial bacteria, involved in the metabolism of plant polysaccharides and vitamins strictly associated with the production of neuroactive

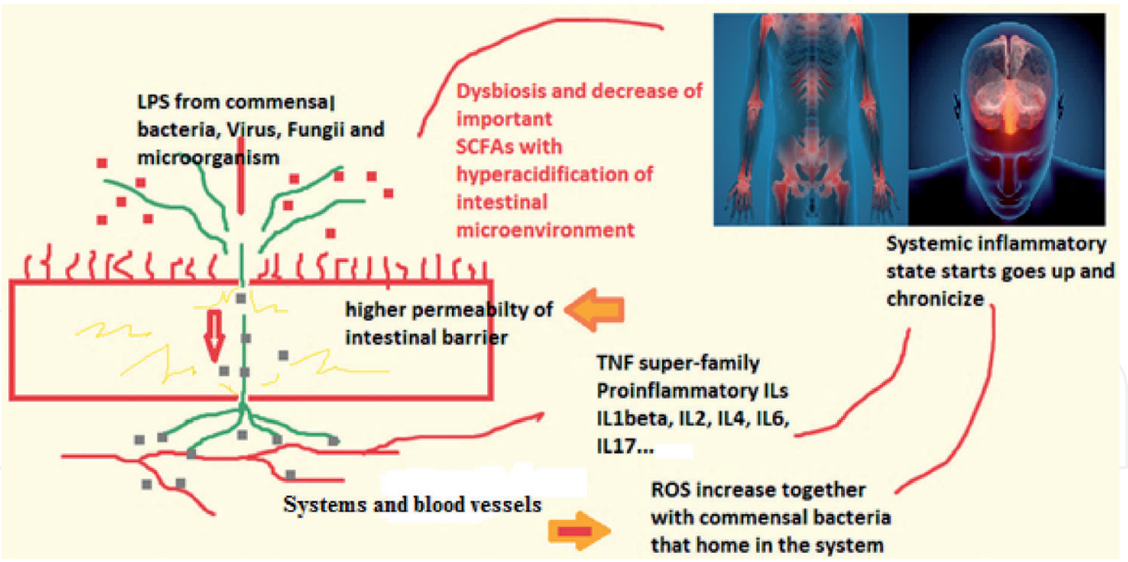

Figure 1.
The gut microbiota is a very dynamic ecosystem. The entire gut microbiota is composed of different sub-environments with unique features like niches with specific microbes and tissue interactions. The large intestine represents the more populated area and performs the highest variety of biotransformation under the guide of specific gene expression in charge of enzymes necessary for highly specific biotransformation necessary of the SCFAs. The local flora is crucial for the local microbiome homeostasis, and the whole chain of bio-reaction takes place in spaces with a specific mean pH of 6.5–7. The changes in local balance homeostasis and in pH negatively impact on the mucosa shield that repair the outside and inside permeability gradient. Once the stability and the equilibrium between all the components are broken, the gut walls become fragile under the constant attack of local immune cells that start to deteriorate the integrity of both endothelial wall and mucosa shield that induce on medium long term and accumulation of pro-inflammatory endotoxins, bacteria free passage into the system, and low antimicrobial peptide production with a consequent high gastrointestinal motility.

SCFAs, such as GABA [20–31]. The *Prevotella* spp. is associated with mucin-type O-glycan production which is extremely important in the integrity of gut epithelial barrier; the absence of this mucin type (mucin-2 specifically) tends to compromise the correct homeostatic balance of the local microbiota, increasing intestinal permeability, a clinical feature associated with both microbial dysbiosis and neurodegenerative diseases [32–34].

Disruption of the BBB is a hallmark in individuals with neurodegenerative diseases that contributes to a steady and progressive death of dopaminergic neurons in the CNS. The BBB is a part of a systemic condition that eventually allows the invasion of pathogens and immune agents from a dysbiotic gut into the CNS. However, damages are also due to a series of changes that weaken the integrity of microvasculature and blood vessels; these modifications are mainly due to nutritional impairment as a consequence of gut microbiota disturbances that cause low-level intake of important nutrients. Deficiencies in vitamins like C, K, D, and folates responsible for low hydroxylation for the formation of chondro-sulfate necessary for healthy microvessel endothelial walls, the augmentation of free radicals, and depletion in oxygen contents and nitrogen, matrix metalloproteinases (MMPs), cyclooxygenases (COXs), and hypoxia-inducible factor-1α (HIF-1α) are all linked with BBB disruption as neuro-inflammatory responses tend to increase and evolve [35].

Thus the scenario existing in the great majority of neurodegenerative pathologies presents a combination of higher permeability of the intestinal barriers and the BBB, inducing a greater access between gut microbiota and the CNS compartment. Experiments conducted with the use of high dose of minocycline antibiotic are well known to have an impact on specific gut and oral invasive bacteria; the post-administration results showed significant protection on LPS-induced PD in mice data confirmed by a significant amelioration of neuro-inflammatory

markers such as TNF-α expression, IL-1α expression, and microglia activation and a substantial amelioration of astrocyte loss with an increased number of surviving dopaminergic neurons compared to control LPS only-injected mice [36, 37]. It follows that a correct use of antibiotics generally known to alter gut microbial diversity may disclose a positive immune protective side effect on inflammatory mechanism existent in PD patients [36–38]. Several other outcomes have shown the beneficial effects of oral antibiotic, minocycline, and tetracycline, in CNS degenerative condition like the experimental autoimmune encephalopathy (EAE) disease and MS. It was found a significant increase of IL-10 expression concomitant with a favorable increase of a subset of invariant NK T cells and in patients with MS, and there was a substantial reduction of CNS deteriorations [38–42].

2.1 Crosslink between microbiota dysbiosis and osteo-decay

Aging brings generally substantial physiological alterations—hormonal, humoral, and physical—that involves the entire homeostatic organization of the human body. Of course the GI tract and its microbiota as well undergo through profound changes that under the variations of dietary influences bring to a general decline of cognitive and immune activities. With aging, the gut microbiota lost bacterial balanced diversity with an increase of "pathogenic Proteobacteria" vs. a continuing, steady, and progressive lower level of "friend bacteria" such as Firmicutes, *Faecalibacterium prausnitzii*, and Actinobacteria (mainly bifidobacteria) [42–45].

Another important feature of gut microbiota is the ability to modulate genes that can be seen either on regulation or variation; this is one of the main factors that may explain the influences that gut microbiota eventually exert on bone development and on bone-related diseases such as osteoporosis, osteopenia, or the different types of arthritis. The delicate homeostatic balance that regulates bone formation and resorption is partly played by the activity of intestinal microorganisms. This activity is basically performed through the interaction with endocrine/nervous system axis; thereby the hormonal activity such as serotonin, cortisol, and sex hormones and several growth factors affect bone mass in mice and humans. In addition, bone marrow stem cells, circulatory stem cells, and stem cells from bone marrow niche are highly sensitive to gut microenvironment condition which eventually affects the differentiation process toward either osteoblasts or osteoclasts. In this case it has been proven that the metabolic pathway compartment which involves the ribosome activity, glycolysis, oxidative phosphorylation, carbon metabolism, and mitochondria ATP are fully responsible of regulating MSCs' functionality, growth, proliferation, and differentiation [45, 46].

This important connection has also been confirmed by Xiao and colleagues; they were able to highlight through the single-cell RNA-sequencing analysis the existing connection between the gut microbiota, BM-MSCs, and bone metabolic functionality. The presence of several factors such as the HIF-1 together with the expression of infection/inflammatory signaling pathways could be the scattering patterns that influence MSC mobility and immunomodulation. These outcomes showed how HIF-1 signaling is involved in BM-MSC immunomodulation. In fact, the HIF-1 is notoriously known as a triggering factor of inflammatory transcription factor NFκB and an active regulator of specific cytokine and chemokine recruitment in inflammation and infection situations. The chronic presence of an inflammatory response under the triggering activity of pro-inflammatory cytokines such as the TNF superfamily IL-1β, IL-2, IL-4, IL-6, and IL-17 can deeply disturb the osteoclast and osteoblast balance, typically resulting in a net hyper-osteoclast activity and

thus bone loss. While there is an evident mechanical effect on the bone where these cytokines stimulate osteoclast differentiation with a consequent upregulation of RANKL expression in progenitor osteoblasts together with a higher RANKL expression, a concomitant nonmechanical effect under the downregulation of specific deficit due to a metabolic inability of vitamin K and vitamin D synthesis in the intestinal lumen should be mentioned (**Figure 2**) [47–54].

2.2 Probiotic efficacy in therapy and clinically use

The potential impact of the therapeutic effect of probiotic on a dysbiotic situation could not be seen without taking in consideration a change of lifestyle. Diet habits, stress, poor healthy conditions, and lack of exercise can significantly impact the gut microbiota stability [55–57]. There are many evidences that nutritional habits based on "Western diet" composed of huge additive and animal fats, processed glucose and excessive quantities of hypercaloric nutritional facts, low contents of fresh food, and low level of vitamins and minerals, essential for our body, all negatively affect the correct balance of gut microbiota, which eventually lead to the insurgence of metabolic dysfunctions. It is also well known that these bad behaviors are associated with an increased risk of developing several chronic diseases that may attack oral microbiota and vaginal microbiota that recent study findings have indicated as an independent risk factor for severe neurodegenerative conditions [9, 58–60].

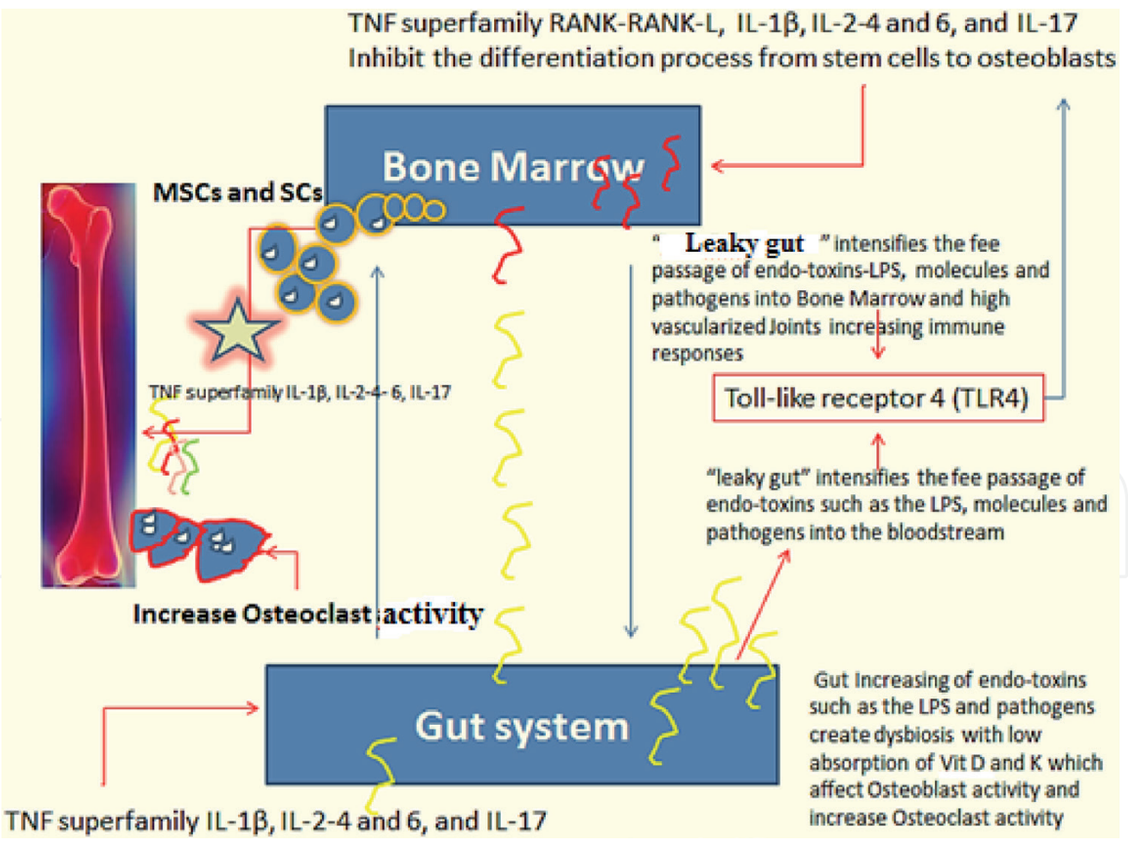

Figure 2.
The gut dysbiosis is one of the main contributors in osteo-degenerative conditions. The dysbiotic microenvironment increase the viability of systemic pro-inflammatory cytokines and interleukins generating three main anti-regenerative patterns, the increase of pH acidic level, decrease of the differentiating pathway from MSCs and SCs toward osteoblasts, and hyper-expression of osteoclast activity. The dysbiosis generates a defective absorption mechanism of important nutrients for bone homeostasis like vitamins, among them K and D, and hormones such as serotonin, testosterone, and estrogen. The prerogative of this condition is a cascade of events that will involve systemically and progressively the whole vital activity of cells, tissues, and systems of the organism.

By definition, probiotic refers to large and diverse types of microbes both commensal that normally reside in the gut and exogenous that may migrate through the intestine following food or diet and supplement consumption. Probiotics might be composed of different microbial strains, the most common include species of *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, and yeast *Saccharomyces* species [61].

As previously mentioned, currently there is a great interest on the use of specific probiotics as therapeutic tool to be associated as clinical approach toward immune system pathologies that may include autoimmune conditions that may attack nerves, bone, and bowel. Given the prevalence of probiotic use, the effects of probiotics on bone health is of significant interest.

Significant positive clinical outcomes have been obtained in numerous studies conducted on CNS inflammatory condition that have therapeutically used different types of probiotic strains. The results showed a reduction of CNS inflammatory level and progression; these outcomes were eventually explained by the capacity of certain strains (*Lactobacillus* species including bacteria like the *Pediococcus acidilactici*, *Bifidobacterium bifidum*, *Bifidobacterium animalis*, *Streptococcus thermophiles*, and *Bifidobacterium infantis* 35,624) to modulate the expression of T-regs, B-regs, and IL-10 production such as [62–64].

In addition, an experiment with genetically engineered microbial strains such as *Lactococcus lactis* capable of expressing heat shock protein 65 obtained from another strain like the *Mycobacterium leprae* was seen highly efficient in reducing EAE symptoms and disease progression [63, 64]. The beneficial outcomes in this study were associated with a decrease in IL-17 pro-inflammatory interleukin with a parallel growth of IL-10 evaluated in the mesenteric lymph node and spleen cell cultures. Furthermore, mice showed a significant higher level of endogenous CD4 + Foxp3+ regulatory T-regs and CD4 + LAP+ (latency-associated peptide). These results might be also sustained by a higher production of SCFAs that, as stated by Opazo and colleagues, were seen to induce either a decrease in RORγt, a biomarker of IL-17, or IL-23 with a higher production of IL-10 and IL-12 with a similar beneficial effect on both EAE and IBS [61–66].

Therefore beneficial homeostatic-metabolic effect of specific probiotic strains can be seen on different systems such as the cardiovascular, immune, and CNS. For instance, few strains conserve a natural ability of inhibiting the insurgence of hypercholesteremia in both mice and human. In fact the use of *Lactobacillaceae* strains such as *L. acidophilus*, *Bifidobacterium bifidum*, and *L. plantarum* Lp9 strain showed a significant role in lowering the cholesterol level under in vivo conditions thanks to their ability of secreting functional bile salt hydrolase (BSH), an enzyme crucial in the protection against the insurgence of bad cholesterol in the host. Genomic analysis has indicated that *Lactobacillaceae* especially *L. plantarum* contain the highest presence of *BSH* genes. Intriguingly, milk fermented by *L. plantarum* NTU 102 revealed to have a high significant efficacy on total cholesterol and LDL cholesterol levels though in presence of individuals undergone a cholesterol-rich diet [67–70].

Major depressive disorders have been seen even today as a consequence of decreased serotonin level; therefore, the therapeutic strategy has mainly concentrated on producing medication, which focused on serotonin only. The major treatments are based on a class of drugs known as selective serotonin reuptake inhibitors (SSRIs). These SSRIs stimulate the serotonin uptake between neurons, and, though it has been seen some improvements, the medium long-term use has produced serious side effects on gut homeostatic balance with severe metabolic disturbances. Nowadays, as above mentioned, following the fact that current researches have established associations between gut microbes, digestive function, and mental well-being especially under the fact that serotonin is synthesized in the gut by the

combined activity of different microbiota strain such as *Lactobacillus*. The connection was firstly seen in IBS patient who also manifests clear clinical signs of depressive disorders; the analysis of gut microbiota from these patients showed a very low level of *Lactobacillus* strains versus healthy subjects that might be explained by the increased expression of serotonin transporter (SERT) [71–74].

Overall the data on this specific topic all have evidenced the positive effects of probiotics in CNS health. These effects are explained by the ability of probiotics to directly interact with fundamental metabolic agents either within the gut or outside that eventually explain the Gut-CNS axis. The use of probiotics and in specific the *Lactobacillus* strains showed that mice fed with these probiotics revealed a better capacity of reabsorbing tryptophan amino acid the precursor or serotonin, the re-established normal level of those hormones strictly related to stress deviances and depression such as the adrenocorticotropic hormone (ACTH), corticosterone, adrenaline, noradrenaline and the re-increase expression of brain-derived neurotrophic factor (BDNF) a marker that indicate a neuronal health and memory functionality [74–79].

To conclude, the higher permeability of gut or "leaky gut" intensifies the fee passage of endotoxins such as the LPS and other forms of molecules and pathogens to leak into the bloodstream and thus in the entire system. The upsurge of these endotoxins, pathogens, and waste molecules eventually trigger the activation of a cascade of immune responses through switching on the Toll-like receptor 4 (TLR4) that mediates the recruitment of T and B lymphocytes together with a huge number of pro-inflammatory cytokines, interleukins, and IgA (**Figure 3**) [80, 81]. The current position therefore considers the use of probiotics as a therapeutic tool that

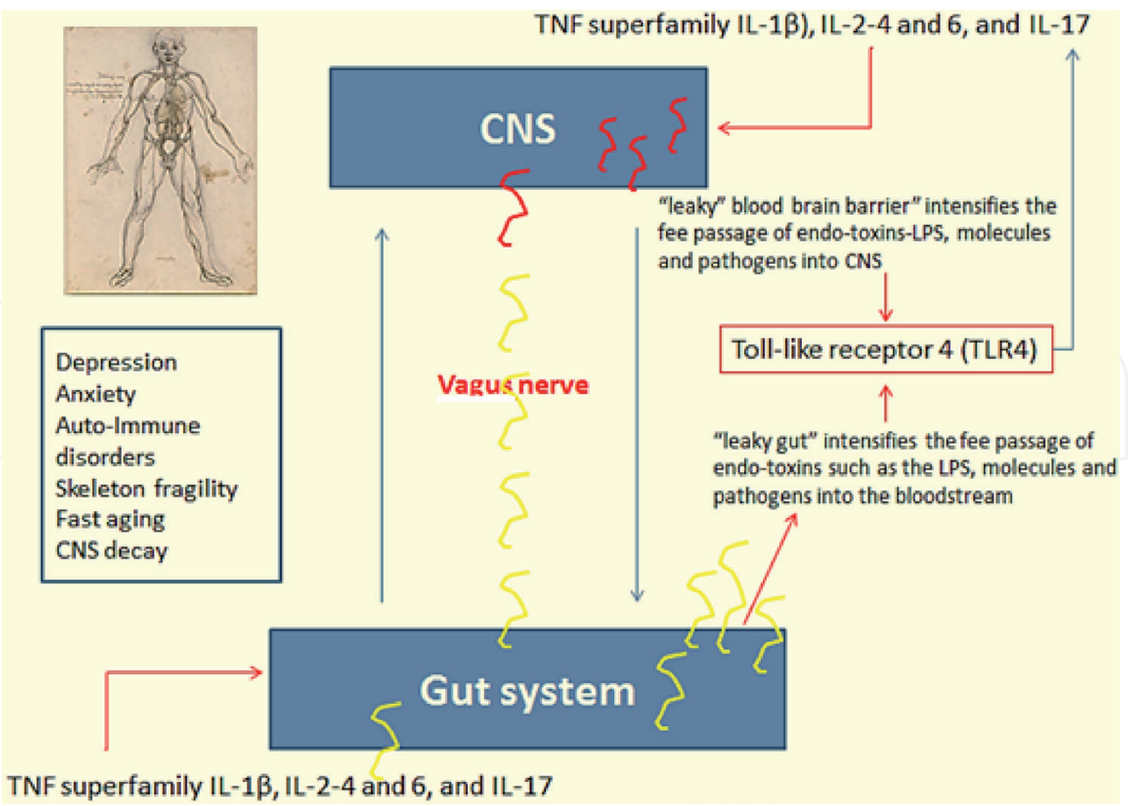

Figure 3.
There is a strict connection between CNS and gut system. The connection takes place through the afferent and efferent pathways of vagus nerve that physically connects both CNS and gut. Both CNS and gut may undergo leaky phenomena; in both cases, the barriers of either CNS or gut become extremely permeable under the chronic attack of both pathogens and immune agents overexpressed on the site. This event may eventually explain degenerative condition of both systems including IBS, ulcerative colitis, depression, PD, AD, and MS.

may exert beneficial effects on the CNS by improving the stability homeostasis and integrity of gut microbiota, decreasing systemic inflammation.

2.2.1 Probiotics in the treatment of skin and oral mucosa dysbiosis

The skin represents another system where an immense variegation of microbiota environment can be found. Skin diseases caused by disturbances at the level of local microbiota that also showed to have strict connection with gut dysbiosis are quite exhaustive in explaining these malevolence patterns. Psoriatic lesions show a very specific histopathological conformation which present highly infiltrated immune cells like the $CD3^+$ T cells and dendritic cells (DCs). Psoriasis showed to have a genetic family trait prevalent in twins; researchers have spotted 36 genetic loci associated with PS susceptibility 1 (*PSORS1*) locus on chromosome 6p21.3 [82, 83]. Data confirmed that most of them are directly involved in the overexpression of those genes that regulate part of pro-inflammatory innate immune responses such as the NFkB activation and interleukin (IL)-23 signaling pathway. Intriguingly a 2018 study performed on mice proved the use of two specific probiotic *Lactobacillus* strains, the *L. salivarius* L305 and *L. rhamnosus* L307, in alleviating the clinical symptoms of psoriasis through inhibiting the aggressive effect of pro-inflammatory cytokines and interleukins like TNF-α, IL-1β, IL-6, IL-17, and IL-22 and promoting the anti-inflammatory/modulatory activity of IL-4 and IL-10 [84].

In oral dysbiosis, we are facing a similar inflammatory arrangement; oral diseases manifest with high-grade inflammatory patterns that spread from the gums to the adjacent structures gradually destroying the supporting tissues of the teeth, both ligaments and alveolar bones, causing early loss. Similarly to psoriasis in periodontitis, we may encounter multifactorial condition due to a combination of genetic variants triggered by the initial subgingival dysbiosis and then become highly susceptible to wider disease progression [85].

The gram-negative bacteria such as *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Aggregatibacter actinomycetemcomitans* are be able to migrate into the system either down to the heart, lungs, and sex apparatus or are capable to enter into the brain via the bloodstream or via infected periodontal sites. Histopathological analysis has confirmed these bacteria almost everywhere in atheromatous plaques, the vagina, amniotic fluid, rheumatoid arthritis bioptic samples, and brain plaques typical of neurodegenerative diseases AD, PD, and MS [86–90].

As can be seen from published studies, different strains of probiotics have been used for the treatment of periodontitis. *Lactobacillus* strains are the commonest used in the majority of high-grade inflammatory disease. The use of *L. salivarius* in combination with *L. rhamnosus* and *B. subtilis* together with *L. reuteri* and *L. brevis* probiotics has shown the most promising results. High-positive results were also obtained by Laleman and colleagues in using *Streptococcus oralis* KJ3, *Streptococcus uberis* KJ2, and *Streptococcus ratti* JH145 [91, 92].

Therefore an associated altered gut microbiota may lead to chronic gut dysbiosis and propagation of systemic injuries that involve cells, tissues, system, and the intrinsic dysfunction of the regenerative mechanism.

3. Conclusion

In summary, the present chapter reveals that gut microbiota and a correct use of probiotic may play important pleiotropic functions on several levels and

systems. It is now clear that there is a bidirectional interaction between microbiota and nervous system, microbiota and immunity, microbiota and bones, and eventually microbiota and mitochondria. Probiotics are getting more and more attention due to the increase of evidence of their benefits in many degenerative disorders. It shows the capacity of microbiota to restore gut and vaginal and oral microbiota, thus attenuating various severe inflammatory responses. All these findings suggest that probiotics could play a role in clinical procedure and therapy approaches to decrease the risk of morbidity and mortality related to CNS diseases, cardiovascular diseases, and bone degenerations. The shared information presented on this chapter may also demonstrate that the traditional view on gut microbiota and microbiome has changed and may be eventually useful as a prospective medium for the delivery of superior, more precise, and personalized treatments in the achievement of better protective health benefits for a more and more aging society.

Conflicts of interest

The authors declare no conflicts of interest.

Author contribution

The authors contributed equally to this work.

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