

Common Inflammatory Mechanisms in COVID-19 and Parkinson's Diseases: The Role of Microbiome, Pharmabiotics and Postbiotics in Their Prevention

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Abstract: In the last decade, metagenomic studies have shown the key role of the gut microbiome in maintaining immune and neuroendocrine systems. Malfunction of the gut microbiome can induce inflammatory processes, oxidative stress, and cytokine storm. Dysfunction of the gut microbiome can be caused by short-term (virus infection and other infectious diseases) or long-term (environment, nutrition, and stress) factors. Here, we reviewed the inflammation and oxidative stress in neurodegenerative diseases and coronavirus infection (COVID-19). Here, we reviewed the renin–angiotensin–aldosterone system (RAAS) involved in the processes of formation of oxidative stress and inflammation in viral and neurodegenerative diseases. Moreover, the coronavirus uses ACE2 receptors of the RAAS to penetrate human cells. The coronavirus infection can be the trigger for neurodegenerative diseases by dysfunction of the RAAS. Pharmabiotics, postbiotics, and next-generation probiotics, are considered as a means to prevent oxidative stress, inflammatory processes, neurodegenerative and viral diseases through gut microbiome regulation.

Keywords: renin–angiotensin–aldosterone system, gut microbiome, coronavirus infection, COVID-19, neurodegenerative diseases, inflammatory processes, oxidative stress, pharmabiotics, probiotics, postbiotics, symbiotics, *Lactobacillus*

Introduction

Inflammation and oxidative stress are common symptoms of neurodegenerative diseases and viral infections such as Parkinson's disease and COVID-19. The immuno pathogenesis induced by SARS-CoV-2 disrupts the immune system, leading to inflammatory responses. It is reported that COVID-19 enters the cell by interacting with the angiotensin-converting enzyme II receptor ACE2 and transmembrane serine protease-2 TMPRSS2.^{1–3} Therefore, serum angiotensin 2 AngII levels increase as a result of its reduced degradation by ACE2. Accumulated AngII has been shown to activate inflammatory cytokines, including interferon-gamma, followed by interferon gene stimulation, resulting in increased cytokine storm and associated acute respiratory distress syndrome, as seen in severe disease.^{1,4–6} Moreover, activation of cytokines leads to hyperactivation of downstream signaling cascades, including nuclear transcription factor kappa B NF-κB, which is usually activated by SARS-CoV-2 itself via pattern recognition receptors.^{1,5,7}

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Elevated levels of reactive oxygen species by SARS-CoV-2 can cause redox imbalances, increase the amount of lipid peroxidation products, and open the transition pores of mitochondrial permeability. Factors such as procaspase, apoptosis initiation factor, and cytochrome C are activated as a result of an electron imbalance in mitochondria.^{1,8-10} These factors contribute to further cell damage, promoting apoptotic cell death.^{1,11-13} Evidence is also accumulating that oxidative stress caused by increased reactive oxygen species production after hypoxia promotes the death of dopamine-containing neurons through apoptosis, which leads to the development of Parkinson's disease, a progressive neurodegenerative disorder.^{1,14-16}

Patients diagnosed with Parkinson's disease do not have dopamine-containing neurons in the substantia nigra compacta and striatum. 6-hydroxydopamine is a well-known neurotoxin that induces neurotoxicity in the nigrostriatal dopaminergic system by inhibiting mitochondrial electronic circuit complexes I and IV and contributing to dopamine-containing neurons' degeneration.^{1,15,17-19} Hence, this leads to a dopamine deficiency and has a strong effect on dopaminergic receptors. Surprisingly, the neurotransmitter dopamine and its receptors have been implicated in the regulation of respiration.^{1,20-22} Moreover, it has been reported that 6-hydroxydopamine is produced endogenously in Parkinson's disease patients.¹ The actual cause of the development and progression of Parkinson's disease is not yet known.¹ Several pieces of evidence suggest that dopamine-containing neurons' death may result from elevated reactive oxygen species levels,^{1,23-25} mitochondrial respiratory failure,^{1,26-28} and activation of the NF- κ B and caspase pathways.^{1,27,29,30}

The development of inflammation and oxidative stress is often accompanied by dysbiosis or dysfunction of the gut microbiome.^{31,32} The gut microbiome plays a vital role in human health and disease and is, therefore, a popular area of research.^{32,33} Lactobacteria^{32,34} are the most important probiotic bacteria in the gut microbiome. Their positive functions include antagonism and competition with opportunistic microorganisms, improving digestion, participating in the maturation of the immune system at an early age and maintaining immunological homeostasis throughout life, neuromodulation, and the production of vitamins and other useful compounds, including antioxidant.^{32,35,36} These bacteria can exhibit significant antioxidant activity in the intestine of the host and promote the production of enzymes and antioxidant compounds that neutralize reactive oxygen species and prevent oxidative damage.^{32,37,38}

However, most of their functions are specific for strains and are not common to several genera or species.^{32,37-39}

The neuromodulatory potential of the human gut microbiome has been studied since the introduction of the gut-brain axis concept. Potential biomarkers that explain the neuromodulatory potential of the gut microbiome have been identified.^{32,40-42} Correction of the intestinal microbiome of patients with inflammatory diseases and oxidative stress characterized by an unbalanced antioxidant system should be carried out using strains of probiotic bacteria with selected antioxidant properties. The gut microbiome of people resistant to oxidative stress can be extracted to find unique strains that can be used to treat patients with chronic inflammatory diseases using a gut microbiome-based approach.³²

The microbiome-gut-brain axis explains the mutual regulation of the nervous system and the gut microbiome through immunological, neurological, and neuroendocrine systems.^{43,44} Imbalance the microbiome-gut-brain axis under adverse factors, such as antibiotics, stress, food quality⁴⁵⁻⁴⁷ weakens the intestinal barrier and cause the formation of pathological processes such as chronic inflammation of the gastrointestinal tract, Alzheimer's disease and neurodegenerative diseases.⁴⁷⁻⁴⁹ It has been shown that inflammation in the gastrointestinal tract increases neuroinflammatory processes,^{50,51} which can be a consequence of the malfunction of the renin-aldosterone-angiotensin system (RAAS).^{52,53} The RAAS is involved in the mechanisms of the formation of inflammatory processes in the human body.^{54,55} The virus COVID-19 uses ACE2 receptors of the RAAS to enter into human cells and launches neurodegenerative processes by RAAS dysfunction.⁵⁶ Understanding the molecular mechanisms of pathogenesis prevents oxidative stress, inflammatory and neurodegenerative processes by correcting the gut microbiome. Probiotic bacteria with antioxidants include lacto- and bifidobacteria, as well as some species of propionic acid bacteria and enterobacteria,⁵⁷⁻⁵⁹ antimutagenic, immunomodulatory, and antitumor properties, can be used for the correction of the gut microbiome in modern methods of therapy.⁶⁰⁻⁶³ In modern therapy, not only do probiotics play an important role, but also postbiotics - their metabolites and components. Lately, pharmabiotics have become popular in medical practice. Pharmabiotics are preparations based on probiotics and their metabolites with a known composition of active substances, deciphered mechanisms of their action, and proven efficacy and safety.⁶⁴⁻⁶⁶

Oxidative Stress and Inflammation Oxidative Stress Characteristics

Oxidative stress is an event caused by an imbalance between the production and accumulation of oxygen reactive species in cells and tissues and the ability of a biological system to detoxify reactive intermediates or repair damages.³² In order to maintain proper cellular homeostasis, a balance must be struck between the production and consumption of reactive oxygen.³² Oxidative stress is caused by the main reactive oxygen species: superoxide radicals, hydroxyl radicals HO⁻, lipid peroxide radicals, and hydrogen peroxide H₂O₂.³²

There are endogenous (product of metabolism and oxidative phosphorylation in mitochondria) and exogenous (negative external factors, as environmental pollution, radiation, drugs, bacterial infection, excessive iron intake, imbalance of the intestinal microbiome) reactive oxygen species.^{32,67–71} The damage of mitochondrial membranes can be because of increasing amounts of reactive oxygen species.³² Some enzymes capable of producing superoxide radicals are redox flavoproteins, xanthine oxidase, NADPH oxidase, and cytochrome P450.^{67,72}

Reactive oxygen species can endanger cell viability by causing DNA hydroxylations, protein denaturation, lipid peroxidation, and apoptosis.^{32,73} Some oxygen reactive species act as cellular messengers in the transmission of redox signals and can disrupt normal cellular signaling mechanisms.^{32,68,70,71} Oxidative stress is a common pathogenetic mechanism of tissue damage that is accompanied by various inflammatory processes and has been linked to a number of diseases including atherosclerosis, cancer, emphysema, liver cirrhosis, arthritis, and diseases with chronic conditions such as cardiovascular, respiratory, and neurodegenerative diseases.^{32,37,71,74} Oxidative stress triggers neurodegenerative brain diseases, Parkinson's disease, amyotrophic lateral sclerosis, and depression.^{32,75–79} Neurodegenerative disorders are associated with the gut microbiome, which is involved in bidirectional communication as part of the gut-brain axis.^{32,80}

To neutralize reactive oxygen species, the human body synthesizes antioxidant enzymes and molecules that form a natural biological antioxidant barrier.³² Antioxidants interact with reactive oxygen species and prevent the disruption of cellular functions.³² The most studied cellular antioxidants are the enzymes superoxide dismutase, catalase, and glutathione peroxidase. Less studied, but no less important, antioxidant enzymes are peroxiredoxins,

sulfiredoxin, paraoxonase, glutathione S-transferase, and aldehyde dehydrogenase.³²

However, reactive oxygen species are not always harmful and can be beneficial as they are used by the immune system as a way to attack and kill pathogens.⁸¹ Short-term oxidative stress may also be important in the prevention of aging by induction of a process named mitohormesis.⁸² Also, reactive oxygen species play an important role in cell signaling, a process called redox signaling.³²

Inflammatory Processes Caused by Viral Infections

Although viruses can replicate in several cell types, the pathological outcome only appears in one or a few tissue-specific cells.⁸³ The primary encounter with the virus occurs in mononuclear phagocytic cells such as monocytes, macrophages, and dendritic cells.⁸³ The stimulation of the innate and adaptive immune system in response to viral infections destroys infected cells, inducing inflammation that may lead to severe pathological consequences for the host. The damage of cells caused by the immune system with a viral infection is known as virus-induced inflammation.^{83–85}

In the earliest stages of viral infection, cytokines are produced when the innate immune defense is activated.^{83,86,87} Neutrophils are among the earliest types of phagocytic cells entering the site of infection and are classic markers of the inflammation process.^{83,86,87} The rapid release of cytokines at the site of infection initiates new reactions with far-reaching consequences, including inflammation.^{83,86,87} One of the first cytokines to be produced is tumor necrosis factor alpha TNF- α , which is synthesized by activated monocytes and macrophages.^{83,86,87} Inflammation is a very noticeable response to TNF- α .^{83,86,87} Inflammation is caused by the excessive release of antibodies, interferons, and pro-inflammatory cytokines, activation of the complement system, or hyperactivity of cytotoxic T cells.

In severe cases of certain viral infections, as in avian influenza H5N1 and coronavirus SARS-CoV-2, aberrant induction of the host immune response can elicit a flaring release of cytokines known as a cytokine storm.^{83,88} There is evidence for the development of progressive multifocal leukoencephalopathy, a fatal human demyelinating disease caused by the John Cunningham virus (JCV), in patients treated with Natalizumab monoclonal antibodies.⁸⁹ The JCV virus is detected in 70–90% of the world's population, which can cause progressive multifocal

leukoencephalopathy in people with weakened immune systems.^{90,91} About 50% of patients with viral multifocal leukoencephalopathy die within a few months after diagnosis. Several studies indicate the association of the Epstein-Barr virus (EBV) with the development of multiple sclerosis.^{89,92} The high incidence of multiple sclerosis in people who have undergone EBV infection may serve as evidence of the primacy of inflammatory processes in the remitting and progressive course of multiple sclerosis.⁹³ Another virus associated with the development of multiple sclerosis is the Human Herpesvirus type 6 (HHV-6), which is involved in triggering autoimmune reactions.^{94–96} An inverse relationship has been found between the age of HHV-6 infection and the risk of developing multiple sclerosis in the future. The MS-associated retrovirus (MSRV) may be transactivated by external risk factors for multiple sclerosis such as HHV-6 and EBV viruses. Thus, various infectious agents (JCV, MSRV, HHV-6, EBV, and SARS-CoV-2), provoking inflammation, can be triggers of progressive neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease, and multiple sclerosis.^{89,97}

Oxidative Stress and Inflammation in the Formation of Neurodegenerative Diseases

Oxidative stress and the inflammatory process it causes are able to form neurodegenerative diseases, including Parkinson's disease and multiple sclerosis.⁹⁸ Chronic inflammation in the small intestine as a result of infection can lead to the activation of glial cells of the enteric nervous system, mainly nerve fibers of the autonomic nervous system, and a violation of the conformational properties of proteins, namely, α -synuclein. Subsequently, the molecules of pathological forms of α -synuclein transynaptically penetrate the central nervous system along the afferent fibers of the vagus nerve and begin to exhibit prion-like properties affecting the dorsal nucleus and neurons of the caudal trunk.^{99,100} Disturbances in the composition of the gut microbiome are closely associated with delayed colonic transit, olfactory dysfunction, emotional-affective disorders, and depression.^{41,101,102}

Multiple sclerosis is a chronic autoimmune neurodegenerative disease in which the myelin sheath of nerve fibers in the brain and spinal cord is affected.¹⁰³ At certain stages, the mechanisms of neurodegeneration in multiple sclerosis and Alzheimer's disease may have common features. The

progression of Alzheimer's disease is associated with the accumulation of the pathological protein β -amyloid and neurofilaments and amyloid plaques formed from it in the brain. In multiple sclerosis, accumulation of the β -amyloid precursor in axons around amyloid plaques was also found, the concentration of which positively correlates with the stage of the disease.⁹³ The neurodegenerative process and inflammation in multiple sclerosis can be enhanced in the case of mitochondrial dysfunction and oxidative injury of neurons. The α -synuclein protein, which is responsible for the development of neurodegeneration, is also involved in the development of multiple sclerosis. The concentration of α -synuclein increases with opticomyelitis and exacerbation of multiple sclerosis.¹⁰⁴ There is evidence of acceleration of the neurodegenerative process under conditions of activation of systemic inflammation.¹⁰⁵

Cytokine Storm and Oxidative Stress Caused by COVID-19 ACE2 Receptors are the Gates for SARS-CoV-2

Viral pandemic coronavirus infection COVID-19 (coronavirus disease 2019) caused by the Severe Acute Respiratory Syndrome-Related Coronavirus 2 (SARS-CoV-2), (<https://www.worldometers.info/coronavirus>) leads to a wide range of functional consequences,¹⁰⁶ capable of infecting most organs and systems in human, including the gut microbiome^{107–109} and central nervous system.¹¹⁰

Penetration into host cells is the first step in viral infection. The entrance gates for the coronavirus are the epithelium of the upper respiratory tract and the epithelial cells of the stomach and intestines.^{109,110} Dissemination of the COVID-19 virus from the systemic circulation or through the plate of ethmoid bone Lamina cribrosa can damage the brain. Changes in olfaction (hyposmia) at an early stage of the disease may indicate damage to the central nervous system and the mucous membrane of the nasopharynx as a result of the inflammatory process.¹¹⁰

The spike glycoprotein on the viral envelope of the coronavirus can bind to specific receptors on the membrane of host cells. Previous studies have shown that ACE2 is a specific functional receptor for SARS-CoV.¹¹¹ It has been shown that SARS-CoV-2 can enter cells expressing ACE2 but not cells without ACE2 or cells expressing other coronavirus receptors such as aminopeptidase N and dipeptidyl peptidase 4, confirming that ACE2 is a cellular receptor for SARS-CoV-2.^{3,111} Further studies have shown that the

binding affinity of the SARS-CoV-2 thorn glycoprotein with ACE2 is 10–20 times higher than that of SARS-CoV with ACE2.^{111,112} The probable mechanism of penetration of SARS-CoV-2 into host cells consists in binding the receptor-binding domain of the spike glycoprotein with the tip of the ACE2 subdomain.^{111–115} The fusion of the viral and host cell membranes is activated upon binding, and the viral RNA is subsequently released into the cytoplasm, causing infection. During SARS-CoV infection, intact ACE2 or its transmembrane domain is internalized together with the virus.^{111,116} The catalytically active site of ACE2 is not overlapped by the thorn glycoprotein, and the binding process does not depend on the peptidase activity of ACE2.^{111,114}

Pathogenesis of SARS-CoV-2

Clinical manifestations of COVID-19 are variable, ranging from mild clinical manifestations to severe illness.^{117,118} Common clinical manifestations include headaches, loss of smell and taste, nasal congestion and runny nose, cough, muscle pain, sore throat, fever, diarrhea, and breathing difficulties.^{119,120} The SARS-CoV-2 virus can infect a wide variety of cells and body systems. COVID-19 is best known for affecting the upper respiratory tract (sinuses, nose, and throat) and the lower respiratory tract (windpipe and lungs).¹²¹ The lungs are the organs most affected by COVID-19, as the virus gains access to host cells through the receptor for the angiotensin-converting enzyme 2 ACE2, which is most abundant on the surface of type II alveolar lung cells.¹²² The virus uses a special surface glycoprotein called a spike to bind to the ACE2 receptor and enter the host cell.¹²³ COVID-19 leads to diffuse damage to the alveoli and inflammatory infiltrates containing lymphocytes in the lungs.^{124,125}

It has been shown that multiple organs are damaged during infection with SARS-CoV-2. After the penetration of the virus, COVID-19 affects the ciliated epithelium of the nasopharynx and upper respiratory tract.¹²⁶ Many people with COVID-19 are known to have neurological or mental health problems. The virus was found in cerebrospinal fluid upon dissection. The exact mechanism by which it enters the central nervous system remains unclear and may initially involve invasion of peripheral nerves, given the low levels of ACE2 in the brain.^{127–129} The virus can also enter the bloodstream from the lungs and cross the blood-brain barrier to gain access to the central nervous system, possibly in infected white blood cells.¹³⁰ The SARS-CoV-2 virus infects the gastrointestinal tract because ACE2 is expressed in high

levels in the glandular cells of the gastric, duodenal, and rectal epithelium, as well as endothelial cells and enterocytes of the small intestine.¹³¹

Although SARS-CoV-2 has a tropism for ACE2-expressing airway epithelial cells, people with severe COVID-19 show symptoms of systemic hyperinflammation. The increased levels of IL-2, IL-7, IL-6, granulocyte-macrophage colony-stimulating factor GM-CSF, interferon-gamma-induced protein 10 IP-10, chemoattractant protein of monocytes 1 MCP1, inflammatory protein of macrophages 1 - alpha MIP-1 alpha, and tumor necrosis factor TNF-alpha, indicative of cytokine release syndrome, suggest an underlying immunopathology.¹³² Also, people with COVID-19 and acute respiratory distress syndrome have classic serum CRS biomarkers, including elevated levels of C-reactive protein CRP, lactate dehydrogenase LDH, D-dimer, and ferritin.¹³³ Systemic inflammation leads to vasodilation, which leads to inflammatory lymphocytic and monocytic infiltration of the lungs and heart. In particular, pathogenic T cells secreting GM-CSF have been shown to correlate with the recruitment of inflammatory monocytes secreting IL-6 and severe lung disease in people with COVID-19.^{125,134}

Cytokine Storm Caused by COVID-19

The severity of the inflammation caused by COVID-19 can be attributed to the severity of the so-called cytokine storm.¹³⁵ Levels of interleukin 1 β , interferon gamma, interferon-induced protein 10, and monocytic chemoattractant protein 1 were associated with the severity of COVID-19 disease. Treatment has been proposed to combat the cytokine storm as it remains one of the leading causes of morbidity and mortality in COVID-19 disease.¹³⁶

The cytokine storm occurs due to an acute hyperinflammatory reaction that causes clinical disease in a variety of diseases, but in COVID-19 this is associated with a worse prognosis and increased mortality.¹³⁷ The hurricane causes acute respiratory distress syndrome, blood clotting phenomena such as strokes, myocardial infarction, encephalitis, acute kidney injury, and vasculitis. The production of IL-1, IL-2, IL-6, TNF-alpha, and interferon-gamma, all essential components of a normal immune response, inadvertently becomes the cause of the cytokine storm. Central nervous system cells, microglia, neurons, and astrocytes are also involved in the release of proinflammatory cytokines that affect the nervous system, and the effects of cytokine storms on the central nervous system are not uncommon.^{137,138}

Oxidative Stress and Systemic Inflammation in COVID-19

Oxidative stress has recently been proposed as a key factor in COVID-19.^{139–141} The mechanism includes the activity of ACE2, which cleaves the octapeptide angiotensin II Ang II, which was previously generated by ACE.¹³⁹ Since Ang II is a potent vasoconstrictor that plays a key role in raising blood pressure, its treatment with ACE2 induces vasodilation, enhanced by the formation of Ang 1–7, a peptide with potent vasodilating functions that are generated during this process.¹³⁹ The binding of SARS-CoV-2 to ACE2 causes the virus to enter cells and, in turn, reduces the bioavailability of ACE2.¹³⁹ Due to the protective function of ACE2, a decrease in its levels is associated with unfavorable clinical phenotypes, and its key role in the pathogenesis of SARS-Cov-2 has been described.^{139,142} Evidence has shown that Ang II regulates the activation of nicotinamide adenine dinucleotide phosphate NADPH oxidase^{143–146} and binds to angiotensin type 1 receptor AT1R.^{139,147} The activation of oxidase is one of the main factors in the formation of reactive oxygen species including the superoxide radical anion O_2^- and hydrogen peroxide H_2O_2 .¹³⁹ Therefore, the decreased bioavailability of ACE2 after SARS-CoV-2 binding allows Ang II to be available to interact with AT1R, which mediates signals for NADPH oxidase activation and induces oxidative stress and inflammatory responses that in turn contribute to the severity of COVID-19.^{139,148,149} It was shown, that NADPH oxidase-2 is overexpressed in hospitalized patients with COVID-19, causing increased oxidative stress.^{139,150}

Inflammation and the immune response Coronavirus subtypes such as SARS-CoV and especially SARS-CoV-2 are capable of actively causing the so-called cytokine storm by mediating the increased production and release of proinflammatory cytokines,¹⁵¹ which confirms the high levels of inflammatory markers found in patients with COVID-19.^{132,139,152–155} Interestingly, one of the identified markers is the nonspecific C-reactive protein, a widely used biomarker for the diagnosis of sepsis.¹³⁹ In addition, elevated levels of inflammatory cytokines and chemokines have been associated with the severity of COVID-19 and death.^{132,139,152–155} Elevated plasma concentrations of interleukins such as IL-1 β , IL-2, IL-6, IL-7, IL-8, IL-10 or IL-17, interferon γ , interferon γ -induced protein 10, chemoattractant monocyte protein 1 MCP1, granulocyte-macrophage colony-stimulating factor, macrophage inflammatory protein 1 α and tumor necrosis factor- α TNF α , among others, have been identified as inflammatory

mediators in COVID-19.^{132,139,156–160} Importantly, macrophages and neutrophils also play a potential pathological role during SARS-CoV-2 infection¹⁶¹ by producing numerous reactive oxygen species including, but not limited to, H_2O_2 , O_2^- , and hydroxyl radical OH.^{139,162} Oxidative stress affects the immune system by altering immune cell function and inflammatory response.^{139,163,164} The systemic cytokine profiles observed in patients with severe COVID-19 are similar to those seen in cytokine release syndromes such as sepsis, with increased production of cytokines such as IL-6, IL-8, TNF α , and other pro-inflammatory chemokines, including chemokine CC ligand 2 CCL2, CCL3 and chemokine CXC ligand 10 CXCL10.¹³⁹

Parkinson's Disease Accompanied by Inflammatory Processes of the Nervous System

Oxidative Stress and Inflammatory Processes in the Parkinson's Disease

Parkinson's disease is a progressive nervous system disorder that affects human movement. The etiology of Parkinson's disease is still a matter of debate,^{165,166} while the number of clinical cases is growing steadily.^{167,168} Parkinson's disease is now recognized as a multisystem disease. The neurochemical and pathomorphological basis of Parkinson's disease is the death of neurons in the substantia nigra of the brain and the subsequent depletion of dopamine reserves in the striatum.¹⁶⁸

One of the theories of the pathogenesis of Parkinson's disease suggests that, as a result of disruption of the functioning of the antioxidant system and increased formation of reactive oxygen species, oxidative stress leads to the rapid accumulation of abnormal conformations of the α -synuclein protein in the affected neurons. The accumulation of the α -synuclein protein in the neurons in amounts exceeding the capacity for its degradation by the proteolytic system leads to the formation of inclusion bodies in the cytoplasm, called Lewy bodies. The main component of Lewy bodies is α -synuclein.¹⁶⁸

The concept of conformational diseases suggests the role of the conformation of a single protein or several proteins in the initiation and progression of Parkinson's disease.^{169,170} Intracellular accumulation of not only α -synuclein but also β -amyloid in the cerebral cortex was detected in patients with Parkinson's disease since stage III according to the Hoehn-Yahr scale.¹⁷¹ Thus, cortical

accumulation of β -amyloid may be a determining factor in the development of the transition from early to late stages of Parkinson's disease.¹⁷¹

It has been shown that parasympathetic neurons of the intestinal submucosa and exogenous alimentary factors such as infectious and toxic are involved in the early stage of development of Parkinson's disease.⁹⁹ There is evidence that a shift in the composition of the gut microbiome may play an important role in the initiation and progression of Parkinson's disease, as a result of the upward diffusion of α -synuclein from the parasympathetic nervous system of the gut to the brain.¹⁷²

Modern Concepts of the Etiology of Parkinson's Disease

Parkinson's disease is currently the second most common neurodegenerative disease, the incidence of which is expected to increase in the coming decades due to increased life expectancy.^{173,174} Although most cases of Parkinson's disease occur sporadically, a small subset of Parkinson's disease cases are hereditary and are attributed to mutations in genes associated with PARK loci including SNCA, Parkin, DJ-1, PINK1, NURR1, OMI/HTRA2, and LRRK2 associated with the disease. Many theories have been proposed for the etiology of idiopathic Parkinson's disease,¹⁷⁴⁻¹⁷⁷ but none of them provide a solid basis for explaining all symptoms. Indeed, some authors shrewdly view Parkinson's disease as a syndrome with various possible etiologies.^{174,178-180} While the exact cause of Parkinson's disease is currently unknown, scientists have come up with the following possible theories of this disease etiology: based on genetics, based on the environment, based on the presence of Lewy bodies, based on the presence of alpha-synuclein in Lewy bodies. According to genetics-based theory, there are certain genes that, when they become mutated, cause Parkinson's disease. However, these mutated genes are very rare, except in cases where Parkinson's runs in the family. There are also some gene variations that seem to slightly increase the risk of developing Parkinson's.¹⁷⁴ According to environment-based theory, there are some environmental factors and toxins which may trigger Parkinson's disease, although they feel the increased risk is small. According to theory based on the presence of Lewy bodies, changes happening within the brain may also be a trigger for Parkinson's disease. Lewy bodies are proteins found in brain cells that are biomarkers of the disease and may

hold the key to finding out the exact cause.¹⁷⁴ According to theory based on the presence of alpha-synuclein in Lewy bodies, alpha-synuclein proteins form clumps in the cells which are thought to contribute to the disease. In the environmental toxin hypothesis, progressive neurodegeneration of Parkinson's disease may be caused by chronic exposure to a neurotoxin or limited exposure to initiate a self-replicating cascade of deleterious events.^{174,181} It is possible that the idiopathic manifestation of Parkinson's disease depends on several factors, such as individual nuclear/cytosolic protein variants, endosymbiont mitochondria, and microorganisms, which will synergistically contribute to the development of the disease.^{174,177,182}

Today, the theory of inflammatory processes initiated by the gut microbiome and the transmission of signals to the intestinal and central nervous systems mediating the vagus nerve is of the greatest interest. According to this theory, the gut microbiome can cause inflammation of the gut and brain, leading to immune-like Parkinson's disease. An imbalanced gut microbiome or a breakdown of the immune system can lead to gut dysbiosis, causing an inflammatory response with the partial movement of intestinal contents into the bloodstream and inevitably to distant parts of the body.^{174,183-185} The central nervous system is protected by the blood-brain barrier, a true barrier and an important mediator of central nervous system homeostasis, which separates the blood from the neuronal parenchyma and insulates the brain from harmful molecules. However, this blood-brain barrier can be disrupted in Parkinson's disease as a result of intestinal dysbiosis, creating a self-reinforcing loop leading to the activation and recruitment of peripheral immune cells and neurodegeneration.^{174,186-189}

The gut microbiome associated with feces and mucous membranes also differs between people with Parkinson's disease and healthy people.^{174,190} In patients with Parkinson's disease, intestinal inflammation is observed,^{174,191} and it has been described that the infiltration of monocytes and T cells into the brain parenchyma is primarily caused by the microbiome associated with the intestinal mucosa.^{174,187,188} These cells appear to be required to control both local inflammatory responses in the brain and the activation of peripheral immune mechanisms.^{174,192} In addition, intestinal infection stimulates mitochondrial antigen presentation and autoimmune mechanisms that target cytotoxic mitochondria-specific CD8⁺ T cells to the periphery and to the brain.^{174,185}

This once again indicates that mitochondria retain the ability to activate the innate immunity of neurons.^{174,182,185} There is also evidence that Parkinson's disease may result from the combined effects of inflammation and asynchronous vagal spread,^{174,177,187} being a common trigger of gut dysbiosis.^{174,177}

Some bacteria contain immunoreactive motifs that are potent IgA inducers, as observed in multiple sclerosis and inflammatory bowel disease.^{174,193} This emphasizes the role of the gut microbiome as the main participant in the dynamic migration of plasma cells between the gut and the brain.^{174,194–196} However, it is interesting to ask why the immune-stimulating bacteria in the gut can lead to the recruitment of regulatory immune cells to the central nervous system.^{174,195,197} It can be explained that a breached intestinal barrier may allow gut microbiome-specific immune cells to act as systemic mediators able to penetrate the central nervous system during acute neuroinflammation.^{174,195,198} Recent reports show that gut-derived IgA plasma cells are present in meningeal venous sinuses of slow blood flow whose fenestrations can potentially allow access of blood-borne pathogens into the brain.^{174,194}

Role of the Raas System in the Pathogenesis of Parkinson's Disease and COVID-19

Involvement of the RAAS System in Systemic Inflammatory Processes

The RAAS is a vital system of the human body, as it maintains plasma sodium concentration, blood pressure, vascular tone, and extracellular fluid volume, carries out tissue remodeling, and produces pro-inflammatory and pro-fibrotic effects. Renin and angiotensin are two of the most important constituents of RAAS.¹⁹⁹ Renin, or angiotensinogenase, is secreted by the granular cells of the kidneys and is found in several isoforms containing 340 amino acids with antagonizing functions.²⁰⁰ Renin is also considered a hormone because it has a signaling function. The enzyme renin acts on its substrate to form angiotensin II, a universal effector peptide hormone.²⁰¹

Angiotensin II is a versatile effector molecule with intracrine, autocrine, and paracrine roles which interacts with all body systems.^{202,203} Angiotensin II is one of the most powerful vasoconstrictors, regulates bronchial smooth muscle contraction, the proliferation of lung fibroblasts, and vascular permeability in the lung tissue,

increases blood pressure and heart rate, stimulates plasminogen activator, inhibits the PAI-1 and PAI-2 proteins, increases the prothrombotic potential, affects the release of prostaglandins and vasoconstriction of the kidneys.²⁰⁴ Cyclooxygenase 1-Derived Prostaglandin E2 and its receptor have been identified as critical for angiotensin-dependent hypertension. Angiotensin II may promote lipogenesis, increase adipose tissue mass, and is associated with fatty inflammation, glucose intolerance, and insulin resistance.²⁰¹ In addition, angiotensin II stimulates the adrenal cortex to secrete aldosterone, a steroid hormone that maintains sodium-potassium homeostasis by stimulating the proximal renal tubules to increase sodium reabsorption and potassium release²⁰¹ (Figure 1).

The most important components of the RAAS system are the angiotensin-converting enzymes ACE and ACE2, whose tasks are the maintenance of the homeostasis of the cardiovascular system, regulation of the systolic pressure, and osmotic and electrolyte balance.²⁰⁴ Despite the similarity of the *ACE* and *ACE2* genes, the ACE and ACE2 enzymes perform different functions in the human body. Angiotensinogen is synthesized in the liver, after which it is converted by renin to angiotensin I, and then converted by an enzyme ACE into angiotensin II. Normally, ACE2 converts angiotensin II to angiotensin 1–7, which causes vasodilation, decreases blood pressure, and participates in

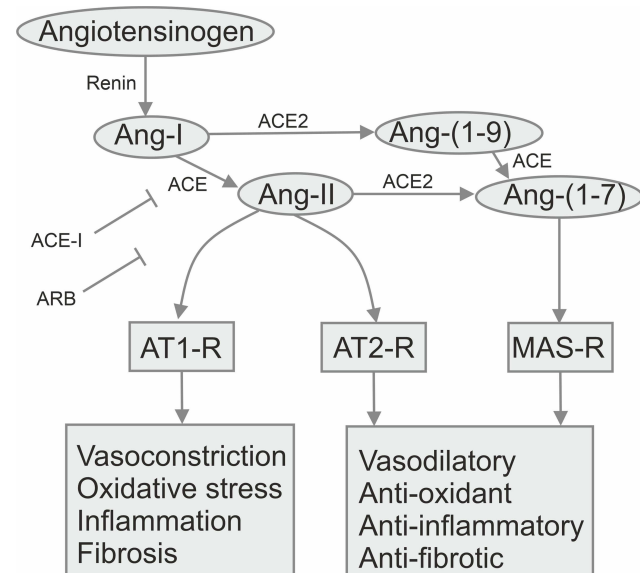


Figure 1 The scheme of the renin–angiotensin–aldosterone system. **Abbreviations:** ARB, angiotensin receptor blocker; ACE-I, ACE inhibitor; AT1-R, the angiotensin II type 1 receptor (AT1 receptor); AT2-R, the angiotensin II type 2 receptor (AT2 receptor); Mas-R, mas receptor; Ang-(1-7), angiotensin-(1–7); Ang-(1-9), angiotensin-(1–9); ACE, angiotensin-converting-enzyme; ACE2, angiotensin-converting enzyme 2; Ang-I, angiotensin I; Ang-II, angiotensin II.

the absorption of neutrally charged amino acids in the gut. Moreover, ACE2 can interact with angiotensin I, converting it to angiotensin 1–9, which can be converted to angiotensin 1–7 under the action of ACE.²⁰⁴

Excessive activation of the tissue system of the RAAS is associated with cardiovascular disease, diabetes, kidney disease, preeclampsia, osteoporosis, and neurodegenerative diseases.^{53–55,205,206} All components of the RAAS have been identified in different areas of the brain at the level of the blood-brain barrier, and the RAAS of the brain is involved in additional brain functions and neurological disorders.^{207,208}

Angiotensin II through type 1 receptors activates the NADPH oxidase complex, which is involved in oxidative stress and inflammatory processes in the pathogenesis of major diseases associated with aging. In the basal ganglia and the nigrostriatal system, hyperactivation of the RAAS through the activation of the NADPH oxidase complex aggravates oxidative stress and the inflammatory response of microglia and promotes the progression of dopaminergic degeneration, which is inhibited by angiotensin receptor blockers and angiotensin-converting enzyme inhibitors.²⁰⁹ An imbalance in renin and angiotensin II can lead to a wide range of chronic and acute diseases. Dopamine depletion leads to increased expression of angiotensin II, which stimulates the synthesis of dopamine, which is released via AT1 or AT2 receptors. In addition, AT1 receptors allosterically inhibit the activation of dopamine D1 receptors. Consequently, the RAAS can play an important modulating role in the flow of information from the cerebral cortex to the basal ganglia. High levels of angiotensin II may enhance neurodegeneration by activating the NADPH oxidase complex, which leads to increased production of reactive oxygen species.²¹⁰ The manipulation of the RAAS, leading to an increase in the expression of ACE2, can affect endocrine functions, which can play an important role in pathological processes.²⁰¹ In addition, ACE2 in the intestine functions as a partner for the amino acid transporter B0AT1. It is possible that the B0AT1/ACE2 complex in the intestinal epithelium regulates the composition and function of the gut microbiome and affects local and systemic antiviral immunity.²¹¹

Chronic activation of the RAAS leads to the onset and development of congestive heart failure syndromes, systemic hypertension, and chronic kidney disease. Excessive levels of circulating and tissue angiotensin II and aldosterone lead to a pro-fibrotic, inflammatory, and hypertrophic

environment that causes remodeling and dysfunction in cardiovascular and renal tissues.²¹²

The Role of the RAAS System in the Pathogenesis of COVID-19

Of particular interest is the interaction of SARS-CoV-2 and the RAAS via angiotensin-converting enzyme 2 ACE2, a receptor used by SARS-CoV-2 to gain access to cells.¹³⁷ The RAAS system includes a carefully balanced and controlled hormone and receptor cascade involving multiple organ systems.¹³⁷ The system is primarily responsible for blood pressure control, maintaining fluid and electrolyte balance, and maintaining systemic vascular resistance.^{137,213}

The RAAS is influenced by estrogen, cortisol, kallikrein-kinin system, Wnt/ β -catenin signaling pathways. It is assumed that the RAAS plays an important role in the pathogenesis of the coronavirus infection COVID-19. A wide range of functional consequences of COVID-19 forced us to pay closer attention to the RAAS.^{214,215} An imbalance in the work of the RAAS under the influence of COVID-19 can provoke an exacerbation of chronic diseases and a development of complications of the cardiovascular system. It has been shown that people with hypertension and an imbalance in ACE/ACE2 levels are likely to have a poor outcome with COVID-19 infection, even with antihypertensive drug treatment.²¹⁶

To fully understand the pathophysiology of COVID-19, it is important to understand the expression and function of ACE2.¹³⁷ It has been shown, COVID-19 has an affinity for the ACE2 cell membrane receptor of the RAAS.^{2,113,137,217–219} The receptor-binding S-protein of COVID-19 has a very high affinity for the ACE2 receptors, which it uses to penetrate human cells.⁵⁶ Penetration of COVID-19 into target cells is a highly regulated multi-step process, where binding to the ACE2 receptor is only the initial stage. ACE2 receptors are found on the cell membranes of the respiratory and gastrointestinal tracts, urinary, cardiovascular, and central nervous systems that are targets for penetration of COVID-19.² However, the main and rapidly achievable target of COVID-19 is the alveolar cells of type II in the lungs, the defeat of which leads to pneumonia.² It is assumed that the greater the number of ACE2 receptors, the more severe the COVID-19 disease progresses. The identification of the membrane receptor ACE2 of the RAAS allows developing further strategies for the treatment of coronavirus infection and

potential therapies to prevent virus penetration into target cells.^{220,221}

Now it is generally accepted that the ACE2 receptor protein is found on the endothelium in various human organs, including the skin, lymph nodes, thymus, bone marrow, spleen, liver, and kidneys, and the brain, as well as the mucous membranes of the mouth and nose, nasopharynx, lungs, stomach, small intestine, and colon, while ACE2 mRNA is found in almost every organ.^{137,217} The most notable finding is the surface expression of the ACE2 protein on alveolar epithelial cells of the lungs and enterocytes of the small intestine.^{137,217} This is especially important when considering the pathogenesis and clinical presentation of patients infected with COVID-19.¹³⁷ Once the cell becomes infected with SARS-CoV-2, ACE2 is internalized and ACE2 expression is reduced.¹³⁷ Therefore, the beneficial degradation of AngII to counter-regulatory Ang (1–7) is reduced, leading to undeniable effects of AngII/AT1,²²² a theory supported by the finding of elevated AngII levels in COVID-19 infected patients.^{137,222,223}

Parkinson's Disease is Accompanied by a Violation of the RAAS System

It is known that the RAAS system may also play a role in Parkinson's disease.²²⁴ Although the exact cause of this progressive neurodegenerative disorder of the basal ganglia remains unclear, it is assumed that inflammation and oxidative stress are key factors in the pathogenesis and progression of the disease.²²⁴ Since angiotensin II is a pro-inflammatory compound that can induce the production of reactive oxygen species due to the activation of the NADPH-dependent oxidase complex, this peptide can contribute to the death of dopaminergic cells.²²⁴ There are three different strategies for intervening in the pathogenesis or progression of Parkinson's disease.²²⁴ These include inhibition of the angiotensin-converting enzyme ACE, blockade of the angiotensin II type 1 receptor AT1, and stimulation of type 2 angiotensin II receptor AT2.²²⁴ Since angiotensin II is a pro-inflammatory compound²²⁵ that activates the NADPH-dependent oxidase complex, the main source of superoxide,^{226,227} it is possible to regulate the progression of Parkinson's disease by manipulating the RAAS system.²²⁴

Allen et al (1992) were the first to suggest a potential link between brain RAAS and Parkinson's disease.^{228,229} These researchers measured a decrease in angiotensin receptor

binding in the substantia nigra and striatum in the postmortem brains of patients with Parkinson's disease.²²⁹ Several studies confirm the important role of ACE in Parkinson's disease.²²⁹ ACE is present in the striped pathway and basal ganglia structures.^{229–231} Patients with Parkinson's disease treated with perindopril, an ACE inhibitor, showed improved motor responses to the dopaminergic precursor 3,4-dihydroxy-1-phenylalanine.^{229,232} ACE has been shown to metabolize bradykinin and thus modulate inflammation, a factor contributing to the development of Parkinson's disease.^{229,233} Activation of the AT1 receptor subtype by AngII promotes the development of nicotinamide adenine dinucleotide phosphate NADPH dependent oxidases, a significant source of reactive oxygen species.^{229,234,235} Treatment with ACE inhibitors has been shown to protect against loss of dopaminergic neurons in animal models of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and 6-hydroxydopamine (6-OHDA).^{229,236–238} The likely mechanism underlying this ACE inhibitor-induced protection is a decrease in the synthesis of AngII acting on the AT1 receptor subtype.^{224,229} It is known that the binding of AngII in the AT1 subtype activates the NADPH oxidase complex, thereby providing the main source of reactive oxygen species.^{229,239–241} In addition, activation of the AT1 receptor leads to stimulation of the NF-κB signaling pathway, facilitating the synthesis of chemokines, cytokines, and adhesion molecules, which are important for the migration of inflammatory cells in the area of tissue damage.^{229,242}

The structures of the basal ganglia have a local RAAS, which indicates increased activity during dopaminergic degeneration.^{229,243–245} Villar-Cheda et al,^{229,246} reported that a decrease in dopaminergic activity caused by reserpine led to a significant increase in the expression of AT1 and AT2 receptors.²²⁹ A similar pattern was observed in 6-OH-dopaminergic dopaminergic denervation, in which a decrease in receptor expression was observed upon treatment with the dopamine precursor 1-DOPA.²²⁹ These results indicate a direct interaction between the RAAS and the dopaminergic system in the structures of the basal ganglia.²²⁹

Common Elements of the RAAS System in COVID-19 and Parkinson's Disease

The RAAS plays a key role in inflammatory processes that affect the microbiome, COVID-19 infection, and the development of Parkinson's disease. The universal role of the RAAS system in the formation of inflammatory

processes leading to many chronic diseases accompanied by inflammatory processes requires further study and more detailed analysis in the post-COVID-19 time. Persistent dysbiosis after COVID-19 can be a factor in multisystem inflammatory syndrome with unpredictable consequences in recovered patients.

SARS-CoV-2 uses ACE2 as a receptor to infect human respiratory epithelial cells.^{247,248} The envelope of the SARS-CoV-2 virus contains the Spike protein with a receptor-binding region that directly binds to the extracellular domain of ACE2.^{248,249} The ACE2 enzyme and its ACE2 receptor are biotargets in the intestinal infection with SARS-CoV-2 and the development of Parkinson's disease. A recent study has demonstrated that the affinity of the S-protein SARS-CoV-2 for human ACE2 is even higher than that of SARS-CoV.^{112,248} Since SARS-CoV-2 must bind to the ACE2 receptor before entering host cells, the distribution and expression of ACE2 may be critical for the target organ of SARS-CoV-2 infection.^{247,248}

Intestinal ACE2 is involved in the transport of amino acids, regulating the composition and function of the microbiome. It has been shown that widespread expression of ACE2 in human tissue may be associated with organ dysfunction, such as lung, kidney, and stomach, in patients with COVID-19.²⁴⁸ However, in Parkinson's disease, the pathogenesis of which is closely associated with old age, ACE2 plays a neurotrophic and protective role, activating the ACE2/Ang-(1-7)/Mas axis, thereby suppressing cognitive impairment. It has been shown that older people are more susceptible to COVID-19 and that older patients with COVID-19 have faster Parkinson's disease progression and higher mortality. Therefore, during the COVID-19 pandemic, it is extremely important to understand the role of ACE2 in Parkinson's disease.²⁴⁸

Several studies suggest that the binding of SARS-CoV-2 to the ACE2 receptor results in ACE2 depletion. This inhibits the ACE2/Ang-(1-7)/Mas receptor pathway and disrupts the balance of the RAAS system. The result is an exacerbation of severe acute pneumonia and cardiovascular complications such as myocardial injury, myocarditis, acute myocardial infarction, heart failure, and arrhythmia in patients with COVID-19.^{248,250,251} ACE2 plays a critical role in the evolution of COVID-19. This is not only a receptor, but it is also involved in post-infectious regulation, including the immune response, cytokine secretion, and viral genome replication.^{248,252} Consequently, target organs prone to developing complications from COVID-19 have some consistency in the

distribution and expression levels of the ACE2 receptor.²⁴⁸ It is well known that ACE2 plays a key role in SARS-CoV-2 infection.^{248,253}

Typical features of Parkinson's disease are the ubiquitous presence of alpha-synuclein-positive Lewy bodies, loss of dopamine neurons, and dystrophic Lewy neurites.^{248,254,255} RAAS also plays an irreplaceable role in brain function, and studies have shown that renin, ACE, Ang II, and Ang (1-7) are found in the central nervous system. They are involved in the regulation of blood pressure, water and food intake, maintenance of the blood-brain barrier, and even in movement, learning, memory, and emotional control.^{248,256} Genetics, epidemiology, and clinical data indicate that overactivation of the RAAS system is one of the main elements of the pathogenesis of neurodegenerative diseases.^{248,256} Moreover, ACE2, including the ACE2/Ang-(1-7)/Mas axis, plays a regulatory role in neurodegenerative diseases.^{248,257} Dysregulation of RAAS is associated with the pathogenesis of Parkinson's disease, and drugs targeting RAAS can improve Parkinson's disease.^{248,258-260} The level of ACE was reduced in the cerebrospinal fluid of patients with Parkinson's disease and negatively correlated with the level of amyloid A β .^{248,261,262} Moreover, electron microscopy has shown that ACE can delay fiber formation in a dose-dependent manner and reduce susceptibility to Parkinson's disease.^{248,263}

ACE and ACE2 have also been found in the cerebrospinal fluid of patients with Parkinson's disease and multiple sclerosis.²⁶⁴ Zubenko et al found a decrease in the level of ACE in the cerebrospinal fluid in patients with Parkinson's disease,^{248,265} and Kawajiri et al revealed a decrease in ACE and ACE2 levels in the cerebrospinal fluid of patients with multiple sclerosis.^{248,266-268} However, there are few studies on the role of ACE2 in the pathological processes of Parkinson's disease and multiple sclerosis, and it is necessary to study the specific mechanism.^{248,269}

Lactobacillus-Based Probiotics for the Prevention of Inflammatory Processes

Classification of *Lactobacillus*

Lactobacillus is a genus of Gram-positive, aerotolerant anaerobes or microaerophilic, rod-shaped, non-spore-forming bacteria of the family Lactobacillaceae, order Lactobacillales, class Bacilli, division Firmicutes. *Lactobacillus* can grow at temperatures ranging from 2°

to 53°C and at pH levels ranging from 3 to 8. The optimum temperature for lactobacteria is 30–40°C, and pH 5.5–6.2. *Lactobacillus* is capable of breaking down carbohydrates, nitrates do not reduce, casein does not break down, gelatin does not liquefy, does not form indole and hydrogen sulfide.³²

The Lactobacillaceae family is one of the most numerous in the bacterial world.²⁷⁰ The Lactobacillaceae family has high phenotypic, ecological, and phylogenetic diversity.²⁷¹ *Lactobacillus* is divided into 26 phylogenetic groups and comprised over 260 phylogenetically, ecologically, and metabolically diverse species, the most famous of which are *L. casei* (*L. casei*, *L. rhamnosus* species), *L. reuteri* (*L. reuteri*, *L. fermentum* species), *L. plantarum*, *L. acidophilus* (*L. acidophilus*, *L. helveticus*), *L. delbrueckii*, *L. brevis*, *L. salivarius*.^{272,273}

Sources for Obtaining Lactobacteria

Lactobacteria are found on plants, in various cavities of animals and humans, in dairy and fermented foods, and organic wastes.²⁷⁴ According to their lifestyle, lactobacteria are subdivided into free-living including ecological and plant isolates, host-adapted including invertebrate or vertebrate hosts, and nomadic species.²⁷⁵ Most of the species of lactobacteria found in the human intestine do not form stable populations and are classified as allochthonous, which are ingested with food. The species *L. plantarum*, *L. casei*, *L. paracasei*, and *L. rhamnosus* are not autochthonous in the classical sense but have an adaptation to the environment of the gastrointestinal tract and oral cavity that allows them to persist there for a long time.²⁷⁶

The most common isolates from the gastric mucosa are *Limosilactobacillus antri*, *Limosilactobacillus gastricus*, *Lactobacillus kalixensis*, *L. reuteri*, and *Lactobacillus ultunensis*. The species *L. crispatus*, *L. gasseri*, *Lactobacillus jensenii*, *Limosilactobacillus vaginalis*, and *Lactobacillus iners* are frequently found in the vagina.^{32,277} A comprehensive study using whole-genome sequencing identified 86 *Lactobacillus* species from 52 non-human feces; 43 of these species were permanent residents in the intestines.^{32,276}

Lactobacteria have always been used by humans for food fermentation, are considered safe for humans, and have been classified as generally regarded as safe GRAS, which can be used as probiotics to maintain health. By

releasing biologically active substances, lactobacteria can prevent pathological conditions such as decreased levels of neurotransmitters, chronic inflammation, oxidative stress, apoptosis, neurodegenerative diseases, ulcerative colitis, inflamed bowel syndrome, and allergies.^{278–282}

Anti-Inflammatory and Antioxidant Potential of Lactobacteria

The ability of certain strains of probiotic bacteria to reduce oxidative stress is widely known and proven in vitro and in vivo. The antioxidant effect of probiotics is due to the production of antioxidant proteins and peptides (superoxide dismutase, thioredoxin, glutathione; proteins that chelate ions Fe²⁺ and Cu²⁺; vitamins (B1, B12, and others; short-chain fatty acids; refolding stress-damaged proteins; modulation of the species composition of the intestinal microbiome.^{32,283} Examples of the antioxidant and anti-inflammatory activity of lactobacteria (Table 1).

Due to the synthesis of biologically active compounds with antioxidant properties, lactobacteria can actively influence the general condition and antioxidant status of the organism.^{59,279,293–295} Some metabolites and components of lactobacteria, like exopolysaccharides and polyphenols, are signaling molecules that affect biochemical processes in the body,^{296–299} reduce the symptoms of dysbiosis and dysfunction of the gastrointestinal tract,³⁰⁰ protect the complex network of neuroglia in the nervous system^{301–304} and have a positive effect on the axes of microbiome-gut-brain and microbiome-gut-lung.^{305,306}

The antioxidant properties of lactobacteria are widely used in the manufacture of functional foods, dietary supplements, and medicines. The study of probiotic bacteria that can prevent the development of oxidative stress and its consequences is an extremely urgent task at present and is of particular importance in the context of the COVID-19 pandemic^{307–311} (Figure 2).

During infection or oxidative stress in human tissues, inflammatory and autoimmune processes are activated with the participation of nuclear factor kappa B (NF-κB). The body's immune response to microbial products during infection with the participation of Toll-like receptor (TLR) leads to increased secretion of lipopolysaccharides, interleukin 1, and tumor necrosis factor-alpha (TNFα), which stimulate the body's antioxidant system by increasing the activity of the enzyme manganese superoxide dismutase (MnSOD),^{310,312,313} while chronically increased secretion

Table 1 Examples of the Antioxidant and Anti-Inflammatory Activity of Lactobacteria

Lactobacillus Species and Strains	Experimental Model	Benefits	Reference
<i>L. plantarum</i>	Female BALB/c mice.	Downregulation of pro-inflammatory cytokines and an increase in anti-inflammatory cytokines in human.	[277,284]
<i>L. rhamnosus</i> CNCM I-3690	HT-29 cells and dendritic cells.	Clear anti-inflammatory profile and increase of viability and average of worm lifespan.	[277,285]
<i>L. reuteri</i> BM36301	C57BL/6 mice.	Anti-inflammatory role and maintaining healthy conditions of mice as they aged.	[32,277,286]
81 lactobacteria strains of 6 different species	<i>E. coli</i> MG1655 strains carrying plasmids encoding luminescent biosensors pSoxS-lux and pKatG-lux.	51 strains demonstrated antioxidant activity.	[32,59]
<i>L. acidophilus</i> ATCC 43121, <i>L. acidophilus</i> ATCC 4356, <i>L. acidophilus</i> 606, <i>L. brevis</i> ATCC 8287, <i>L. casei</i> YIT 9029, <i>L. casei</i> ATCC 393, <i>L. rhamnosus</i> GG	The human cancer cells.	Heat-killed cell of <i>L. acidophilus</i> 606 and <i>L. casei</i> ATCC 393 exhibited the most profound inhibitory activity in the all of tested cell lines; the soluble polysaccharides components of <i>L. acidophilus</i> 606 evidenced the effective anticancer activity.	[32,287]
<i>L. brevis</i> MG000874	Albino mice exposed to D-galactose-induced oxidative stress.	The treated animals displayed improvement in superoxide dismutase, catalase, and glutathione S-transferase in all tissues, as well as glutathione in the liver and serum.	[32,288]
<i>L. fermentum</i> U-21	C57/BL6 mice, <i>C. elegans</i> exposed to paraquat-induced oxidative stress.	The lifespan of the <i>C. elegans</i> was extended by 25%. <i>L. fermentum</i> U-21 ensured normal coordination of movements and the safety of dopaminergic neurons in the brain.	[32,289]
<i>Lactobacillus brevis</i> 47 f	The Balb/c mice with 5-fluorouracil induced mucositis and oxidative stress.	Protects the murine intestine from enteropathy induced by 5-fluorouracil and prevent of lipid peroxidation in the gut tissues and in the blood plasma.	[290]
<i>L. plantarum</i> A7 (KC 355240, LA7)	24 type2 diabetic kidney disease patients.	Oxidized glutathione concentration was significantly reduced; the levels of glutathione, glutathione peroxidase, and glutathione reductase were significantly increased; no significant reduction in the 8-iso-prostaglandin F2 α , malon dialdehyde.	[32,291]
<i>L. acidophilus</i> , <i>L. casei</i>	Diabetic hemodialysis patients, 28 cases and 27 placebos.	Patients who received probiotic supplements showed significantly decreased plasma glucose, serum insulin, assessment-estimated insulin resistance and beta-cell function and HbA1c, insulin sensitivity, serum C-reactive protein, plasma malon dialdehyde, and total iron-binding capacity. Patients showed an increase in plasma total antioxidant capacity.	[32,292]

MICROBIOME SOURCES

HUMAN DISEASES

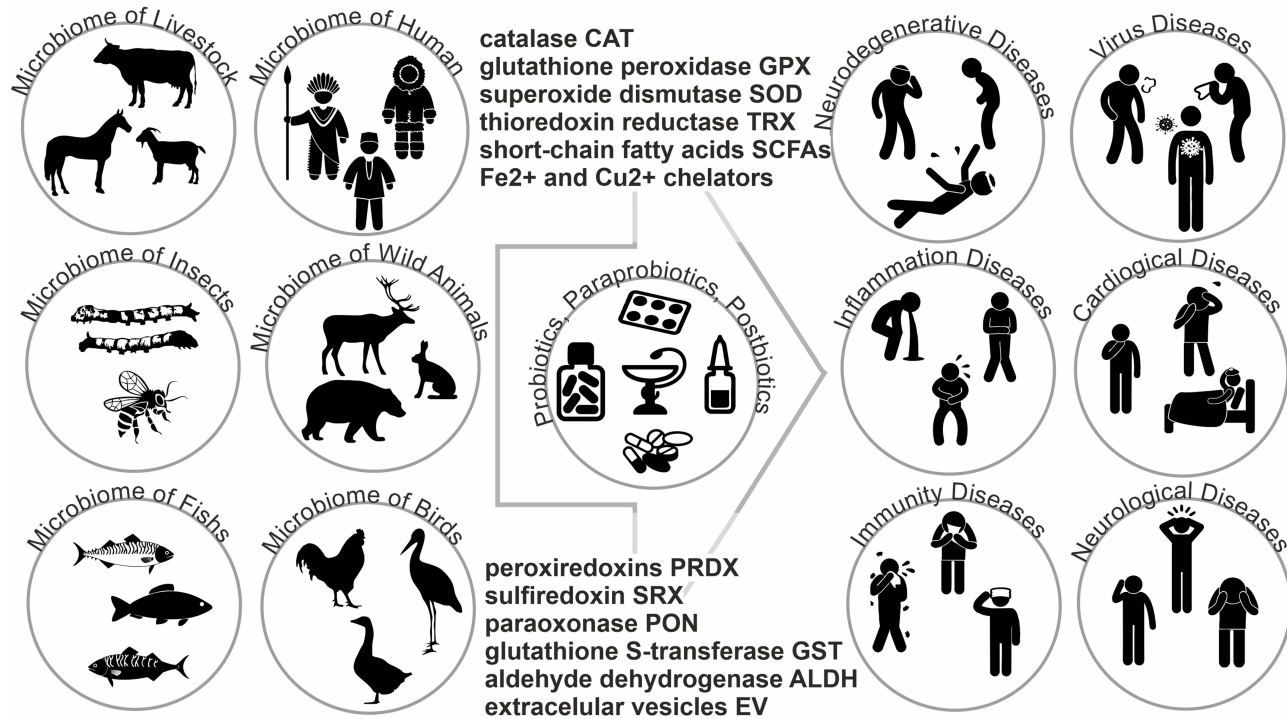


Figure 2 Lactobacteria from the different microbiome sources and the possibilities of their use as probiotics or pharmabiotics, and postbiotics in the prevention and therapy of the human diseases.

of these compounds is triggered autoimmune and neurodegenerative processes in the body.³¹⁴ It has been shown that lactobacteria in the gut microbiome can reduce inflammatory and autoimmune processes by activating the proliferation of regulatory T cells, decreasing the TLR activity and levels of TNF α and proinflammatory cytokines.^{315–318}

Inflammation and oxidative stress in the intestine disrupt the function of the intestinal barrier, as a result of which the number of toxins and metabolites entering the bloodstream, causing inflammation and oxidative stress in organs and tissues, increases.^{319,320} Lactobacteria of the gut microbiome can prevent inflammation and oxidative stress in organs and tissues by reducing oxidative stress caused by hydrogen peroxide molecules, hydroxyl, and superoxide radicals in the intestine through the production of substances with antioxidant activity, such as thioredoxin reductase, superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, glutathione S-transferase, thiols (cysteine and glutathione), exopolysaccharides.^{59,278,279,321–325} Lactobacteria's ability to synthesize antioxidant enzymes, thiols, and exopolysaccharides varies by species and strain and determines their increased antioxidant potential.^{326–332}

The knowledge accumulated in recent years about the antioxidant activity of lactobacteria makes it possible to formulate requirements for an ideal strain that reduces oxidative stress in the body. An ideal probiotic drug capable of reducing cytokine storms and oxidative stress in viral infections and COVID-19 should have the following characteristics.^{283,333–335} The probiotic strain should have direct antioxidant activity and have a complex effect on the innate immune and antioxidant systems of the human body. The probiotic strain must be a natural and complementary component of the human intestinal microbiome. The probiotic strain must have the ability to mildly mobilize the antioxidant potential of the target cells of the human body.³³⁴ The probiotic strain must be able to regulate the concentration of reactive oxygen species in the targeted organs of the body, for example, in the lungs. The probiotic strain must be capable of detoxifying the lipids, proteins, and other components damaged by reactive oxygen species in human cells.³³⁵ The probiotic strain should help restore the intestinal and blood-brain barriers that prevent the penetration of toxicants into the bloodstream and the brain. The probiotic strain should contribute to the restoration of the gut microbiome, which is an important

organ that determines the immunomodulatory and antioxidant potential of a human.^{59,289,333–335} These properties are possessed by the probiotic strain of *Lactobacillus fermentum* U-21, which is capable of synthesizing a complex of antioxidants with proven high antioxidant activity against superoxide anion. Biologically active compounds obtained from the biomass and culture medium of the *L. fermentum* U-21 strain also have antioxidant activity against superoxide anion and can be used in pharmacology and medicine in the treatment of neurodegenerative diseases induced by oxidative stress, as well as in cosmetology with an increase in antioxidant status of skin.^{59,289,290,333–335}

Microbiome Disruption in Parkinson's Disease and COVID-19 Altered Microbiome Composition in Parkinson's Disease

Metagenomic studies show changes in the species composition of the gut microbiome of people with various diseases compared with healthy people.^{336–341} Changes in the structure of the gut microbiome can be observed in humans with diseases such as obesity and metabolic dysfunction,³⁴² allergies, and autoimmune disorders,^{343–345} intestinal inflammation, irritable bowel syndrome, allergic gastroenteritis and necrotizing enterocolitis,³⁴⁶ type 1 and 2 diabetes,³⁴⁷ atherosclerosis,³⁴⁸ asthma³⁴⁹ neurodegenerative diseases including Parkinson's disease.³⁵⁰ Experimental and clinical studies have revealed changes in the structure of the human gut microbiome as a result of degenerative diseases,²⁸¹ depression,^{351,352} and autism,^{41,353} which are accompanied by inflammatory processes.^{354–356}

Currently, several studies are aimed at identifying differences in the microbiome of patients with Parkinson's disease compared to healthy control people.³⁵⁰ While most of them used fecal samples as a proxy for microbiome composition in the distal colon, some examined mucosal opportunistic pathogens or even saliva and nasal mucosa samples.^{350,357–359} The species of the Prevotellaceae family from the Bacteroidetes phylum have been implicated in the pathogenesis of inflammatory bowel disease¹⁹³ and have dramatically decreased in the stool of patients with Parkinson's disease^{190,193,337,338,360–364} and in the sigmoid mucosa.^{350,357,365} It has been reported lower Bifidobacteriaceae levels in patients with Parkinson's

disease.^{338,350} It was found a lower content of Bifidobacteriaceae both in the mucous membrane and in the feces^{350,357,366} and the saliva^{350,367} of patients with Parkinson's disease compared to controls, while others described the opposite.^{350,362,368,369} In a mouse model of Rotenone-induced Parkinson's disease, the number of Bifidobacteriaceae in the cecal and mucous membrane was reduced compared to control mice.^{350,370} It was found an increased content of Lactobacillaceae,^{350,362–364,366,367,369,371} and Erysipelotrichaceae,^{350,359,364,372} in the saliva and the stool of patients with Parkinson's disease compared to the control group whereas some other studies found decreased content of Lactobacillaceae^{338,350,372} and Erysipelotrichaceae^{338,350,357,369} in the stool of patients with Parkinson's disease compared with healthy controls. The genera *Roseburia*,^{338,357,366} *Blautia*^{338,357,366,369} and *Faecalibacterium*^{190,357,369} and *Dorea*^{337,338,357} were less abundant in the stool of patients with Parkinson's disease.³⁵⁰ Genus *Akkermansia* was common in the stool of patients with Parkinson's disease.^{190,338,350,357,359,364,366,373} *Akkermansia muciniphila* can induce different T cell responses depending on other species present in a given microbiome.^{350,374} Also, it has been reported the increasing the viruses in the stool. Stool from patients with Parkinson's disease.^{338,350}

Altered Microbiome Composition in COVID-19

It has been published that COVID-19 patients had an altered gut microbiome compared to the control group.^{375–379} Using a shotgun for metagenomic sequencing of fecal samples it is described dysbiosis in the bacterial microbiome and mycobiome in patients with COVID-19 compared with healthy control patients.^{375,376,379} Notably, COVID-19 patients generally had an increased number of opportunistic pathogens, a portion of the commensal microbiome that can become pathogenic in the event of a host disorder such as dysbiosis or a compromised immune system.^{379,380} Opportunistic pathogens included *Clostridium hathewayi*, *Actinomyces viscosus*, and *Bacteroides nordii* at the time of hospitalization with SARS-CoV-2.³⁷⁹ It is shown that the number of specific opportunistic pathogens, *Collinsella aerofaciens* and *Morganella morganii* spp. was increased in fecal samples with a high level of active viral transcription and

replication of SARS-CoV-2 compared to fecal samples from healthy patients.^{376,379} Conversely, fecal samples with low or no SARS-CoV-2 infectivity had elevated levels of bacteria belonging to *Parabacteroides*, *Bacteroides*, and Lachnospiraceae that produce short-chain fatty acids, especially butyric acid.³⁷⁹ Short-chain fatty acids are known to play an important role in enhancing host immunity. Thus, these data suggest that opportunistic pathogens pose a threat to both a decrease in host immunity and opportunistic infections in proportion to the burden of SARS-CoV-2.³⁷⁹ In another cohort, reduced bacterial diversity was described in fecal samples from patients with COVID-19 compared to healthy controls by analyzing the V3-V4 region of the 16S rRNA gene.^{377,379} The study also found an increase in opportunistic pathogens such as *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces* among COVID-19 patients.³⁷⁹

One gut microbiome study based on 16S rRNA in COVID-19 patients showed that alpha diversity in these patients was lower than in healthy controls and the abundance of four genera: *Streptococcus*, *Clostridium*, *Lactobacillus*, and *Bifidobacterium*, tended to increase, but five other genera, *Bacteroides*, *Roseburia*, *Faecalibacterium*, *Coprococcus*, and *Parabacteroides*, showed lower numbers in COVID-19 patients than in controls.^{378,379} Dysbiosis with decreased levels of *Lactobacillus* and *Bifidobacterium* has been observed in some COVID-19 patients.^{378,379,381} It was shown that the composition of the fecal mycobiome in 30 hospitalized patients with COVID-19 was heterogeneous; however, some had been enriched with the fungal pathogens *Candida* and *Aspergillus* spp. compared to control.^{375,379}

It has shown the potential importance of Firmicutes species in the severity of SARS-CoV-2 infection. It is assessed the association between the fecal microbiome and the severity of COVID-19 in seven patients.^{379,382} A total of 23 bacterial taxa were significantly associated with the severity of COVID-19, and the majority (15 of 23) was of the type Firmicutes. Of these, eight classes (*Coprobacillus*, *Clostridium ramosum*, and *C. hathewayi*) were positively correlated with the severity of the disease, and seven were negatively correlated.^{375,379,383}

The feces of COVID-19 patients were enriched with opportunistic pathogens known to cause bacteremia, including *Clostridium hathewayi*, *Actinomyces viscosus*, and *Bacteroides nordii*^{375,376} due to the disturbed microbial ecology of the intestine and resistance to colonization.^{376,384,385} It showed a similar pattern of gut

microbiome dysbiosis in patients with COVID-19.^{376,386} The number of butyrate-producing bacteria such as *Faecalibacterium prausnitzii*, *Clostridium butyricum*, *Clostridium leptum*, and *Eubacterium rectale* was significantly reduced in patients with COVID-19 compared with the control group.^{376,386} When patients with COVID-19 were compared to the control group, the number of common opportunistic microorganisms Enterobacteriaceae and Enterococcus was significantly higher.^{376,386} At the birth level, the genera of *Streptococcus*, *Rothia*, *Veillonella*, and *Actinomyces* (all opportunistic microorganisms) were enriched with feces from patients with COVID-19, while the deliveries of *Romboutsia*, *Faecalibacterium*, and *Fusicatenibacter* were enriched with feces from healthy people.^{376,377} The content of opportunistic bacteria *Coprobacillus*, *Clostridium ramosum*, and *Clostridium hathewayi* in the feces of patients during hospitalization was associated with COVID-19 disease, while the anti-inflammatory bacterium *Faecalibacterium prausnitzii* showed a negative correlation,³⁷⁵ which suggests a baseline calibration of the intestinal microbe-host immunity, thereby influencing the disease response to SARS-CoV-2 infection.³⁷⁶ Evidence is accumulating that a significant number of COVID-19 patients experienced systemic and organ-specific disease during follow-up after resolution of the disease, including fatigue, muscle weakness, sleep problems, anxiety, depression, diarrhea, and poor glycemic control.^{132,376,387–389} The long-term dysbiosis of the gut microbiome is also consistently observed in patients after COVID-19,^{375,390–392} which means that the gut microbiome is closely related to the health of the host.³⁷⁶

The Role of Microbiome in the Prevention and Treatment of COVID-19 and Parkinson's Disease

The microbiome and its specific components, including lactobacteria, determine the formation and maintenance of innate and acquired immunity, as well as antioxidant potential. Violation of the composition (signature) of the microbiome - dysbiosis, leads to increased sensitivity to infectious and neurological diseases. The immune status of different groups of the population has different indicators: first of all, patients with type II diabetes, autoimmune diseases, AIDS.³² Stressful conditions (social, physical, chemical, nutritional changes) always lead to dysbiosis of the microbiome and a decrease in immune homeostasis.

Analysis of the state of the microbiome is an important biomarker of the state of the immune and nervous system and susceptibility to neurological and infectious diseases as COVID-19.^{32,393,394} The intestinal microbiome influences the host organism due to its ability to synthesize various biologically active compounds. The whole system functions as a single network. A breakdown in one link leads to the failure of the entire system^{32,41,319,393,395} (Figure 3).

The gut microbiome is an organ that integrates the interaction of all body systems and protects against stress factors and infections, including virus infections like COVID-19. It has been shown the coronavirus infection COVID-19 leads to disruption of the gut microbiome and development of dysbiosis.³⁹⁶ Further, dysbiosis leads to inflammation and oxidative stress, which increases the rate and risk of developing chronic diseases.

The symbiotic gut microbiome is important for human health, physiology, and metabolism.^{343,397,398} The biodiversity of the microbiome of a healthy adult is counted in hundreds of different types of microorganisms.^{399,400} More than 600 different species of bacteria related to each other by symbiotic and antagonistic interactions can be found in the gut microbiome of an adult human.^{324,401} The composition of the gut microbiome differs between individuals, although Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia are usually predominant in the human gut.⁴⁰² The composition of the human gut microbiome can be influenced by factors such as food quality, smoking, age, body weight, health status, antibiotics, and habitat.^{403,404} The gut microbiome synthesizes many biologically active substances, such as amino acids, vitamins, neurotransmitters, hormones, and hormone-like substances that can affect the human body, penetrating the bloodstream through the intestinal

barrier.^{400,405–410} The gut microbiome functions as a “virtual endocrine organ” that regulates metabolic signaling pathways of the human body.^{398,410–412}

Some probiotics and postbiotics, as a result of modulation and restoration of the gut microbiome, reduce dysbiosis, systemic inflammation, and oxidative stress in humans.^{413,414} There is evidence that probiotics and postbiotics have potential in the prevention and treatment of Parkinson’s disease, as they support the composition of the gut microbiome, reduce oxidative stress and inflammation, and produce essential biologically active metabolites.^{47,49} As a result of reducing dysbiosis with the use of probiotics, the protective function of the intestine is restored, the systemic inflammatory process is decreased, and the concentrations of uremic toxin, p-cresol, urea, and phosphates in the blood are decreased,^{415–417} the lipid profile in the liver is normalized,^{111,418} the oxidative stress and inflammation in muscles are reduced by increasing the activity of antioxidant enzymes,⁴¹⁹ the learning and memory are increased as a result of eliminating oxidative stress and neurodegenerative processes in the hippocampus,^{111,420–422} the oxidative stress in the heart and blood vessels is reduced by a decrease in the concentrations of NADPH oxidase 2 (Nox2) and T helper 17 cells (Th17), the polarization of regulatory T cells is increased,⁴²³ the basal glycemia and insulin resistance are decreased.⁴²⁴

Viruses that can infect both intestinal epithelial cells and symbiotic microorganisms have a significant effect on the composition of the intestinal microbiome.^{376,425,426} The gut microbiome is the primary antiviral barrier, which, using the CRISPR-Cas system, provides effective protection of symbiotic bacteria from various DNA and RNA viruses, phages, as well as COVID-19.^{425,427,428} One of the mechanisms of antiviral defense of the gut microbiome is a complex of exosomes of bacterial and human

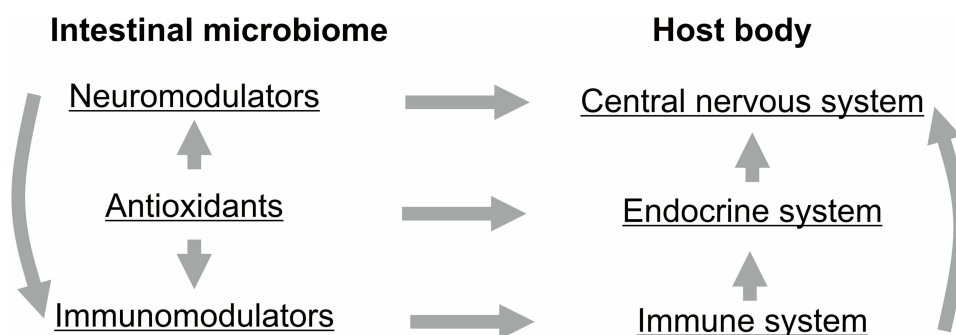


Figure 3 The intestinal microbiome influences the host organism due to its ability to synthesize various biologically active compounds.

origin. Exosomes can capture viral particles, including COVID-19, and carry them into bacterial cells, where they are destroyed.^{429–432} Another mechanism of antiviral defense of the intestinal microbiome is the production of peptides and biologically active metabolites that can prevent viruses from entering cells. Microorganisms of the gut microbiome can synthesize peptides that are able to competitively bind to ACE2 cell receptors, block them from binding to COVID-19 and protect the intestinal epithelium from coronavirus infection and subsequent inflammatory processes.⁴³³ It has been shown that bifidobacteria, in particular *Bifidobacterium longum* GT-15, can reduce intestinal inflammatory processes by producing the type-III fibronectin domain-containing protein (FN3) that binds to a pro-inflammatory agent such as tumor necrosis factor α TNF α .^{434,435} The gut microbiome of people resistant to coronavirus infection is a promising source of *Lactobacillus* strains capable of producing peptides and other active metabolites that prevent the penetration of COVID-19 into human cells and decrease the severity and pathogenesis of this new coronavirus.

Perspectives

It is necessary to develop additional antioxidant and immunomodulatory pharmabiotics, postbiotics, and next-generation probiotic drugs for the prevention and treatment of COVID-19 infection. To create new generation pharmabiotics, and postbiotics, it is necessary to study the intestinal microbiome of stress-resistant people as a resource of biologically active compounds and strains of lactobacteria that ensure human resistance to coronavirus infection. After coronavirus infection and before vaccination, it is necessary to diagnose the state of the intestinal microbiome and normalize the disturbed state. To increase the effectiveness of protein vaccines against coronavirus infection, it is necessary to develop adjuvants based on lactobacteria and bifidobacteria capable of enhancing the cellular immune response.⁴³⁶

Recently, much attention has been paid to the search for new promising sources of lactobacteria with antioxidant properties from the gut microbiome of animals. Thus, the honey bee *Apis mellifera*, closely associated with human life, can be a promising source of beneficial strains of probiotic lactobacteria. Such prospects are related to the fact that bees can survive the winter without flying and empty their guts for 6 months due to their unique adaptation.⁴³⁷ The adaptation of bees to a long winter is provided by the combined antioxidant potential of the organism and the gut microbiome of bees,

which slows down and prevents excessive oxidation of the substrate and protects the organism from oxidative stress.⁴³⁷

Lactobacteria species *Lactobacillus Firm-4 and Firm-5*, *L. helveticus*, *L. kunkeei*, *L. helsingborgensis*, *L. kimbladii*, *L. mellis*, *L. mellifer*, *L. melliventris*, *L. apis*, *L. kullaberme*, *L. johnsonii*, *L. micheneri*, *L. timberlakei*, *L. quenuiae*, and *L. plantarum* are represented in the gut of honey bees in the greatest diversity and are characterized by an enhanced antioxidant potential.^{158,438–440} The antioxidant potential of lactobacteria may be associated with the expression of antioxidant enzyme genes such as catalase, thioredoxin reductase, catalase, glutathione reductase superoxide dismutase, glutathione S-transferase, as well as other products with antioxidant properties, such as lipoteichoic acid.^{158,441}

In the gut of wintering honey bees, the number of lactobacteria species with enhanced antioxidant potential, such as *L. mellifer*, *L. apis*, and *L. melliventris*, is increased.^{439,442} Ochratoxin A causes histopathological changes and liver and kidney dystrophy in rats. It was shown that rats fed with *L. kunkeei* probiotic bacteria from the honey bee gut microbiome have an increased protective potential against oxidative stress caused by ochratoxin A.⁴³⁶ Polystyrene microplastic exposure led to significant decreases in the α -diversity of the honey bee gut microbiome, accompanied by changes to the core microbial population structure and oxidative stress. *Lactobacillus* spp. play a protective role against polystyrene microplastics exposure by stimulating the expression of antioxidative *CAT*, detoxification *CYPQ1* and *GSTS3*, and immune system-related *Domeless*, *Hopscotch*, and *Symplekin* genes in the midgut.⁴⁴³ In the gut of honey bees, *Lactobacillus* species of *L. plantarum* (strains H28, H24, KX519413, KX519414, LP8, LP25, LP86, LP95, LP100) and *L. kunkeei* were characterized by an increased antioxidant potential that protects against different pesticides.^{436,440,444–446} All of these strains of lactobacteria from the gut of honey bees with an increased antioxidant potential can be selected as perspective strains for creating pharmabiotics.⁴⁴⁵

There are new prospects for the use of components of lactobacteria, rather than their use in living form cultures. Postbiotics are now defined as metabolites and cellular components that provide health benefits.^{32,447,448} Postbiotics are a promising area of research for future pharmaceuticals and functional foods with antioxidant properties for the treatment of depressive disorders.^{32,393} The potential of postbiotics can be used by packaging them into nanostructures, allowing them to be delivered to organs affected by inflammation.^{32,449} The use of extracellular vesicles of gram-positive probiotic bacteria, which can freely enter the

bloodstream, as well as tissues and organs of the human body, is another interesting area of research.^{32,450,451} As a modern method, metagenomics is widely used not only to study differences in the composition of the microbiome in disease states in comparison with healthy people, but also to study the functional genes of the intestinal microbiome.³² For this reason, it is desirable to use metagenomic analysis of sequenced whole genome bacterial DNA to study the antioxidant potential of the intestinal microbiome. This approach can yield significant results in the search for target genes that are included in the catalog of reference genes of the search tool.³²

Conclusion

Inflammatory processes of various organs and systems accompany many chronic and infectious human diseases. As a rule, they are accompanied by a violation of the composition and functions of the human intestinal microbiome, called dysbiosis of the intestinal tract. At the same time, inflammation and dysbiosis, having common indicators and mechanisms, are characterized by biomarkers characteristic of certain pathologies. The search for biomarkers of pathologies at the level of the microbiome and the human body is a step towards the practical diagnosis of the disease and the development of drugs. In the case of COVID-19 and Parkinson's disease, the RAAS system is the common system involved in the pathogenesis of diseases properties.³² Angiotensin-converting enzyme 2 ACE2 and its receptor are overlapping bio targets in SARS-CoV-2 and Parkinson's disease. The RAAS system was discovered and described over 100 years ago. It was demonstrated that the RAAS is involved in the formation of oxidative stress and inflammatory processes in viral and neurodegenerative diseases, and the intestinal microbiome performs a protective function of the body. The participation of the RAAS system in the inflammatory processes of all human organs and systems, caused by Parkinson's disease and COVID-19, has been shown. The involvement of the RAAS in complications after COVID-19 requires further research and detailed analysis. The apparent link between gut microbiome dysbiosis and COVID-19 and Parkinson's disease requires the targeted creation of pharmabiotics and postbiotics to correct the microbiome. Using the antioxidant potential of lactobacteria is undoubtedly the right approach in the prevention of inflammatory diseases. Lactobacteria are promising candidates for anti-inflammatory and antioxidant drugs.^{32,452,453} The term pharmabiotics, which was first published about 15 years ago,

better describes probiotic-based medicines.^{454, 455, 456, 457} The development of drugs aimed at eliminating the inflammation phenotype of the intestinal microbiome will be greatly facilitated if new methodological and conceptual approaches to the search for unique strains of probiotic bacteria are implemented; they include a comparative analysis of the genomes of lactobacteria, as well as metagenomes properties.³² Omics technologies have been used to study the intestinal microbiome of healthy people and patients with chronic inflammatory diseases. Characterization of the gut microbiome in health and disease is likely to become possible when the biomarkers of a dysfunctional microbiome are better understood. Efforts are being made to identify the genes responsible for the gut microbiome's neuromodulatory and immunomodulatory properties.³² The development of projects for the study of unique strains of lactobacteria from new promising sources using omics technologies is considered a necessary task of modern health care properties.³²

Disclosure

The authors report no conflicts of interest in this work.

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