**Review / Обзор**
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# Prospects for microbiome modulation in autoimmune diseases: a literature review

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## Abstract

Autoimmune diseases are characterized by dysregulation of immune responses and damage to healthy body tissues. Their complete cure remains elusive, and existing therapies are often accompanied by side effects. Recent studies have shown a significant role of disturbances in the composition of the microbiome in the development of autoimmune reactions. Moreover, modulation of the microbiome through various therapeutic interventions represents a promising direction in the framework of complex therapy of the underlying disease. Extracellular vesicles, in particular exosomes, transport biologically active substances between cells, and a number of studies have shown their therapeutic effect in autoimmune diseases. However, the role of extracellular vesicles in modulating the microbiome remains poorly understood, and further research is needed to better understand their impact on the pathogenesis of autoimmune diseases and associated microbiome changes, as well as to develop new treatment strategies. The presented literature review, based on a study of English-language sources, examines the importance of the microbiota of different loci of the human body (intestines, skin, oral cavity) in the development of autoimmune diseases such as multiple sclerosis, psoriasis and Sjögren's disease. The role of extracellular vesicles in modulating the microbiome during autoimmune diseases therapy is discussed.

**Keywords:** exosomes; intestinal microbiota; skin microbiota; oral microbiota; multiple sclerosis; psoriasis; Sjögren's disease

**MeSH terms:**
AUTOIMMUNE DISEASES – MICROBIOLOGY
AUTOIMMUNE DISEASES – PHYSIOPATHOLOGY
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REVIEW

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# Перспективы модуляции микробиома при аутоиммунных заболеваниях: обзор литературы

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## Аннотация

Аутоиммунные заболевания (АИЗ) характеризуются дисрегуляцией иммунных реакций и поражением здоровых тканей организма. Их полное излечение остается труднодостижимым, а существующие методы терапии часто сопровождаются побочными эффектами. Последние исследования показали значимую роль нарушений состава микробиома в развитии аутоиммунных реакций; более того, модуляция микробиома посредством различных терапевтических вмешательств представляет собой перспективное направление в рамках комплексной терапии основного заболевания. Внеклеточные везикулы, в частности экзосомы, переносят биологически активные вещества между клетками, и в ряде работ был показан их лечебный эффект при АИЗ. Однако роль внеклеточных везикул в модуляции микробиома остается недостаточно изученной, поэтому для более глубокого понимания их влияния на патогенез АИЗ и связанных с ним изменений микробиома, а также для разработки новых стратегий лечения необходимы дальнейшие исследования. В представленном обзоре литературы на основании изучения англоязычных источников рассматривается значение микробиоты разных локусов организма человека (кишечника, кожи, ротовой полости) в развитии таких АИЗ, как рассеянный склероз, псориаз, болезнь Шёгрена. Обсуждается роль внеклеточных везикул в модуляции микробиома при терапии АИЗ.

**Ключевые слова:** экзосомы; микробиота кишечника; микробиота кожи; микробиота ротовой полости; рассеянный склероз; псориаз; болезнь Шёгрена

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ВНЕКЛЕТОЧНЫЕ ВЕЗИКУЛЫ – ИММУНОЛОГИЯ
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**Abbreviations:**
AD – autoimmune diseases
CNS – central nervous system
EVs – blood-brain barrier
IL – interleukin
MS – multiple sclerosis
MSCs – multipotent mesenchymal stromal cells
SD – Sjögren's disease

| HIGHLIGHTS | КЛЮЧЕВЫЕ ПОЛОЖЕНИЯ |
|---|---|
| Metabolites of the gut microbiota – short-chain fatty acids, urolithin A and indoles – are able to restore the permeability of the intestinal barrier in multiple sclerosis by preventing the entry of immune cell-activating compounds into the blood. | Метаболиты микробиоты кишечника – короткоцепочечные жирные кислоты, уролитин А и индолы – способны восстанавливать проницаемость кишечного барьера при рассеянном склерозе, препятствуя проникновению в кровь соединений, активирующих иммунные клетки. |
| Changes in the skin microbiome can serve as an indicator of the phototherapy and biologic therapy effectiveness for psoriasis. | Изменения в микробиоме кожи могут служить индикатором эффективности фототерапии и биологической терапии при псориазе. |
| Antibiotic therapy aimed at modulating the oral microbiota normalizes the level of dysbiosis-associated metabolites and can alleviate the symptoms of Sjögren's disease. | Антибиотикотерапия, направленная на модуляцию микробиоты полости рта, нормализует уровень дисбиоз-ассоциированных метаболитов и может облегчать симптомы болезни Шёгрена. |
| One of the promising therapeutic agents for the treatment of autoimmune diseases are extracellular vesicles – synthesized by cells membrane nanoparticles that are involved in many physiological and pathological processes. | Одним из многообещающих терапевтических средств для лечения аутоиммунных заболеваний являются внеклеточные везикулы – синтезируемые клетками мембранные наночастицы, вовлеченные во множество физиологических и патологических процессов. |
| In the context of therapeutic effects and direct influence on the immune system, there has been a notable emphasis on human cell-derived extracellular vesicles, contrasting with the predominant focus on bacterial vesicles regarding their impact on the microbiome. | В контексте терапевтического эффекта и прямого влияния на иммунную систему в большей мере обсуждаются внеклеточные везикулы клеток человека, в то время как влияние на микробиом показано главным образом для бактериальных везикул. |

Autoimmune diseases (ADs) encompass a diverse array of pathological conditions stemming from immune dysregulation, wherein cytotoxic cells or autoantibodies damage the body's tissues. These conditions significantly diminish patients' quality of life, potentially leading to disability or even death. Despite some notable advancements, treating autoimmune diseases remains a challenge, spurring increased interest in developing novel therapies [1, 2].

In recent years, there has been a growing focus on exploring the human microbiome's role in maintaining the homeostasis of organisms. Numerous researchers have underscored the complex and dynamic ecosystem's influence on immune response modulation and the onset and progression of autoimmune reactions [3] and specific studies have linked gut microbiota with systemic lupus erythematosus [4, 5], type I diabetes [6], multiple sclerosis [7], and rheumatoid arthritis [8, 9]. Moreover, emerging evidence implicates skin and oral microbiota in AD development [10–12]. Therapeutic interventions targeted at microbiota modulation at various sites, including antibiotic therapy, probiotics, and microbiota transplantation from healthy donors, have demonstrated clinical efficacy in AD treatment [13–25] (Figure).

Among the promising therapeutic modalities are extracellular vesicles (EVs), membrane nanoparticles synthesized by cells, capable of regulating various pathophysiological processes in the body. Based on their biogenesis, EVs are classified into apoptotic bodies, exosomes, and microvesicles, distinguished by their formation mechanism, size, and specific markers [26].

The most extensively researched type of EVs are exosomes, which are formed through the double invagination of the parent cell membrane and typically measure 30–150 nm in diameter. Exosomes have shown efficacy in experimental multiple sclerosis (MS) models, also known as autoimmune encephalomyelitis, and using exosomes from human bone marrow-derived multipotent mesenchymal stromal cells (MSCs) led to a significant increase in newly formed and mature oligodendrocytes, along with a higher proportion of anti-inflammatory M2 macrophages [27]. Similarly,

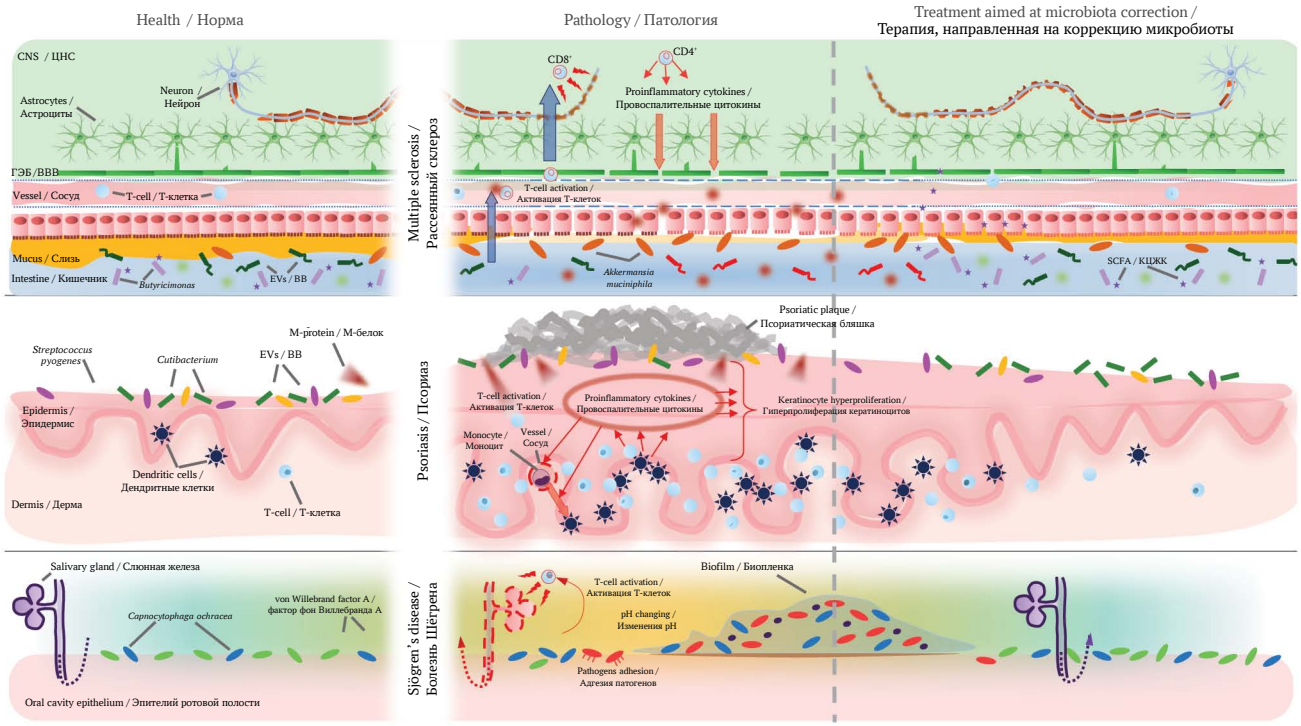


**FIG.** The role of the microbiome in the pathogenesis of several autoimmune pathologies.
In multiple sclerosis, an increase in the number of *Akkermansia muciniphila* bacteria in the intestine may lead to increased mucus and intestinal barrier permeability, which promotes the entry of compounds that activate immune cells into the blood. On the other hand, stimulating the growth of microbiota synthesizing short-chain fatty acids, such as bacteria of the genus *Butyricimonas*, may contribute to the restoration of both intestinal and blood-brain barrier permeability and alleviate disease symptoms. M-protein secreted by *Streptococcus pyogenes* bacteria in psoriasis and von Willebrand factor A secreted by *Capnocytophaga ochracea* bacteria in Sjögren's disease contribute to the activation of T cells producing proinflammatory cytokines.

**РИС.** Роль микробиома в патогенезе ряда аутоиммунных заболеваний.
При рассеянном склерозе увеличение числа бактерий *Akkermansia muciniphila* в кишечнике может приводить к повышению деградации слизи и проницаемости кишечного барьера, что способствует поступлению в кровь соединений, активирующих иммунные клетки. С другой стороны, стимулирование роста микробиоты, синтезирующей короткоцепочечные жирные кислоты, например бактерий рода *Butyricimonas*, может способствовать восстановлению проницаемости как кишечного, так и гематоэнцефалического барьеров и облегчать симптомы заболевания. М-белок, выделяемый бактериями *Streptococcus pyogenes* при псориазе, и фактор фон Виллебранда А, выделяемый бактериями *Capnocytophaga ochracea* при болезни Шёгрена, способствуют активации Т-клеток, продуцирующих провоспалительные цитокины.

Note: CNS – central nervous system; BBB – blood-brain barrier; EVs – extracellular vesicles; CD – cluster of differentiation; SCFA – short-chain fatty acid.
Примечание: ЦНС – центральная нервная система; ГЭБ – гематоэнцефалический барьер; ВВ – внеклеточные везикулы; CD – cluster of differentiation, кластер дифференцировки; КЦЖК – короткоцепочечные жирные кислоты.

in another study, exosomes from human bone marrow MSCs, stimulated with interferon-gamma, reduced inflammation, and demyelination in the central nervous system (CNS) while elevating regulatory T-cell levels in the spinal cord [28]. Regulatory T cells, a distinct subset of T-helper cells, play a pivotal role in maintaining balanced immune responses by curbing excessive inflammation in ADs [29].

Research into imiquimod-induced psoriasis murine models revealed that exosomes from human embryonic MSCs reduced interleukin-17 (IL-17) expression and C5b-9 complement system protein levels in the skin [30] while exosomes from human umbilical cord MSCs inhibited keratinocyte hyperproliferation and decreased Psoriasis Area and Severity Index (PASI) scores [31]. The administering of human umbilical cord blood mononuclear EVs reduced acanthosis and boosted regulatory T-cell content in psoriatic skin in mice [32].

In a murine model of Non-Obese Diabetes (NOD) with autoimmune salivary gland damage, akin to Sjögren's disease (SD), human labial gland MSCs-derived exosomes decreased inflammatory infiltration and enhanced salivary secretion [33]. Additionally, vesicles derived from human induced pluripotent stem cells skewed macrophages in the spleen toward an anti-inflammatory M2 phenotype and decreased T-helper 17 cell numbers [34].

Researchers highlight diverse molecular mechanisms underlying the therapeutic effects of EVs, involving vesicular proteins, lipids, or EV-transferred microRNAs. However, their potential impact on the microbiome in ADs has been scarcely discussed. It is noteworthy that discussions regarding their therapeutic effects and direct influence on the immune system primarily focus on human cell-derived EVs whereas microbiome modulation is mainly demonstrated for bacterial vesicles [27, 28, 30–41].

This review aims to examine the role of microbiota at various sites in the human body in AD development and the potential for its modulation. We investigated the roles of gut microbiota, exemplified by MS; skin microbiota, illustrated by psoriasis; and oral microbiota, showcased by SD. Additionally, we delve into the role of EVs and their prospective use in modulating the microbiome in AD therapy.

This review used English-language sources from PubMed and Scopus from 1995 to 2023, with two-thirds of the sources being articles published within the last five years. The search employed keywords and phrases such as "exosomes", "extracellular vesicles", "autoimmune diseases", "psoriasis", "multiple sclerosis", "autoimmune encephalomyelitis", "Sjögren's syndrome", "Sjögren's disease", "microbiome", "skin microbiota", "gut microbiota", and "oral microbiota".

This review is intended for physician-researchers interested in developing innovative therapies for autoimmune diseases.

## THE ROLE OF GUT MICROBIOTA IN THE DEVELOPMENT OF MULTIPLE SCLEROSIS

MS is a chronic autoimmune neurodegenerative disease characterized by damage to the myelin sheaths of the CNS nerve fibres, leading to motor, sensory, and cognitive impairments, ultimately resulting in disability and sometimes death [42, 43]. Recent estimates suggest that globally, 2.3 to 2.8 million people suffer from MS [44, 45], with the disease predominantly affecting young working-age individuals, which carries not only social but also economic consequences [46]. Despite the development of disease-modifying therapies for MS [47], the disease is still considered incurable.

In MS, effector T cells are activated and penetrate through the blood-brain barrier (BBB) into the CNS, where they reactivate [48]. $CD8^+$ cytotoxic T cells, sensitized to myelin antigens, exert direct cytotoxic effects, while $CD4^+$ T helper cells, particularly Th1 and Th17 populations, contribute to further inflammation progression by synthesizing pro-inflammatory cytokines. Specifically, Th1 cells produce interferon-gamma [49], while Th17 cells produce IL-17 promote microglial cell activation [50, 51] and contribute to BBB destabilization [52], leading to an increased influx of inflammatory cells into the CNS [53]. B cells also play a role in the pathogenesis of MS, through the formation of autoantibodies [54, 55] and cytokines (predominantly in the primary progressive MS type), as well as through antigen presentation to T cells (in the relapsing-remitting course of the disease) [48].

Dysbiosis of the gut microbiota has been repeatedly described in the literature both in patients with MS (see table) and in animal models of autoimmune encephalomyelitis [7, 56–61]. However, there is still no definitive answer to whether dysbiosis is a consequence or one of the triggers of the disease [56, 58]. Notwithstanding, the significance of the gut microbiota in the development of MS is recognized by the scientific community, and the possible mechanisms of complex interactions between the gut microbiota, immune and nervous systems along the gut-brain axis are widely studied.

Increased BBB permeability, and increased intestinal barrier permeability are observed in MS, possibly contributing to the penetration of immune-activating compounds into the blood and influencing the development of inflammation in the CNS [62, 63]. In mouse models of the disease, signs of increased gut permeability were observed as early as day 7 of the experiment, before neurological symptoms appeared [62].

It is assumed that in MS, it is the gut microbiota that contributes to the disruption of gut permeability, both through the loss of some bacteria and through the overgrowth of others due to dysbiosis [64]. For example, bacteria such as *Akkermansia muciniphila* degrade mucins – glycoproteins of mucus covering the intestine. Under normal conditions, this process promotes intestinal barrier renewal and strengthening [65], but in MS excessive proliferation of these bacteria disrupts the balance between mucus formation and degradation, leading to increased gut permeability [66]. On the other hand, the number of *Butyricimonas* bacteria, which produce butyrate (a short-chain fatty acid capable of restoring gut barrier permeability), is decreased in MS patients [67].

It has been shown that metabolites of many colonic commensal bacteria can directly influence the pathogenesis of MS, for instance, the aforementioned short-chain fatty acids, products of dietary fibre fermentation, can restore not only intestinal barrier permeability but also BBB permeability [68]. The ability to restore gut barrier permeability has also been demonstrated for urolithin A and indoles [69–71]. Indoles, bacterial metabolites of tryptophan, can also influence astrocytes through aryl hydrocarbon receptors, reducing inflammation in the CNS [72] whereas in polysaccharide A, a product of *Bacteroides fragilis*, induction of $CD4^+$ T helper cells into IL-10-producing regulatory $FOXP3^+$ T cells has been

***Table*. Changes in the composition of microbiota in multiple sclerosis, psoriasis, and Sjögren's disease**
***Таблица.* Изменения в составе микробиоты при рассеянном склерозе, псориазе и болезни Шёгрена**

| Phylum / Тип | | Class / Класс | Order / Порядок | Family / Семейство | | Genus / Род | | Disease / Болезнь |
|---|---|---|---|---|---|---|---|---|
| *Actinomycetota (Actinobacteria)* | ↑ [59] | *Coriobacteriia* | *Eggerthellales* | *Eggerthellaceae* | ↑ [60] | *Eggerthella* | ↑ [60] | MS / PC |
| | | | | | | *Adlercreutzia* | ↓ [61] | |
| | ↓ [86] | *Actinomycetes* | *Propionibacteriales* | *Propionibacteriaceae* | | *Cutibacterium* | ↓ [86–89] | |
| | | | *Micrococcales* | *Micrococcaceae* | | *Kocuria* | ↓ [88] | P / П |
| | | | *Mycobacteriales* | *Corynebacteriaceae* | | *Corynebacterium* | ↑ [86] | |
| | ↑ [109, 110] | *Actinomycetes* | *Actinomycetales* | *Actinomycetaceae* | | *Actinomyces* | ↓ [111] | SD / БШ |
| | | | *Micrococcales* | *Micrococcaceae* | | *Rothia* | ↓ [111] | |
| *Bacillota (Firmicutes)* | ↓ [59] | *Clostridia* | *Lachnospirales* | *Lachnospiraceae* | | *Blautia* | ↑ [60, 61] | MS / PC |
| | | | | | | *Anaerostipes* | ↓ [59] | |
| | | | | | | *Dorea* | ↑ [61] | |
| | | | *Eubacteriales* | *Clostridiaceae* | | *Hungatella* | ↑ [60] | |
| | | | | *Oscillospiraceae* | ↓ [60] | *Faecalibacterium* | ↓ [59] | |
| | ↑ [86, 89], ↓ [90] | *Bacilli* | *Lactobacillales* | *Streptococcaceae* | | *Streptococcus* | ↑ [86] | P / П |
| | | | *Bacillales* | *Staphylococcaceae* | | *Staphylococcus* | ↓ [87, 90], ↑ [86, 88] | |
| | ↑ [109, 110, 112–114] | *Bacilli* | *Lactobacillales* | *Streptococcaceae* | | *Streptococcus* | ↑ [112], ↓ [109, 110] | SD / БШ |
| | | | *Bacillales* | *Gemellaceae* | | *Gemella* | ↑ [109] | |
| | | *Negativicutes* | *Veillonellales* | *Veillonellaceae* | | *Veillonella* | ↑ [109–112] | |
| | | *Clostridia* | *Peptostreptococcales* | *Peptostreptococcaceae* | | *Peptostreptococcus* | ↓ [111] | |
| *Bacteroidota (Bacteroidetes)* | ↓ [59] | *Bacteroidia* | *Bacteroidales* | *Tannerellaceae* | | *Parabacteroides* | ↓ [61] | MS / PC |
| | | | | *Prevotellaceae* | | *Prevotella* | ↓ [59–61] | |
| | | | | *Odoribacteraceae* | | *Odoribacter* | ↓ [60] | |
| | | | | | | *Butyricimonas* | ↓ [7] | |
| | | | | *Barnesiellaceae* | ↓ [60] | *Barnesiella* | ↓ [60] | |
| | ↑ [86] | *Chitinophagia* | *Chitinophagales* | *Chitinophagaceae* | | *Flavisolibacter* | ↓ [91] | P / П |
| | ↑ [113, 114] | *Bacteroidia* | *Bacteroidales* | *Porphyromonadaceae* | | *Porphyromonas* | ↓ [111] | SD / БШ |
| *Pseudomonadota (Proteobacteria)* | | *Gammaproteobacteria* | *Pseudomonadales* | *Pseudomonadaceae* | | *Pseudomonas* | ↑ [61] | MS / PC |
| | | | *Pasteurellales* | *Pasteurellaceae* | | Haemophilus | ↑ [61] | |
| | | *Alphaproteobacteria* | *Hyphomicrobiales* | *Rhizobiaceae* | | *Mycoplana* | ↑ [61] | |
| | ↓ [86], ↑ [87, 89] | *Alphaproteobacteria* | *Hyphomicrobiales* | *Methylobacteriaceae* | | *Methylobacterium* | ↓ [91] | P / П |
| | | *Betaproteobacteria* | *Burkholderiales* | *Burkholderiaceae* | | *Lautropia* | ↑ [89] | |
| | | | | | | *Cupriavidus* | ↓ [91] | |
| | | | | *Sphaerotilaceae* | | *Caldimonas (Schlegelella)* | ↓ [91] | |
| | ↓ [109, 110, 113, 114] | *Gammaproteobacteria* | *Pasteurellales* | *Pasteurellaceae* | | Haemophilus | ↓ [109–111] | SD / БШ |
| | | *Betaproteobacteria* | *Neisseriales* | *Neisseriaceae* | | *Neisseria* | ↓ [111] | |

*Продолжение таблицы*

| Phylum / Тип | | Class / Класс | Order / Порядок | Family / Семейство | Genus / Род | | Disease / Болезнь |
|---|---|---|---|---|---|---|---|
| *Verruco-microbiota* | ↑ [7] | *Verrucomicrobiae* | *Verruco-microbiales* | *Akkermansiaceae* | *Akkermansia* | ↑ [7, 60] | MS / РС |
| *Euryarchaeota* | ↑ [7] | *Methanobacteria* | *Methano-bacteriales* | *Methano-bacteriaceae* | *Methano-brevibacter* | ↑ [7] | |
| *Fusobacterio-ta (Fuso-bacteria)* | ↓ [89] | | | | | | Р / П |
| *Cyanobacte-riota (Cyano-bacteria)* | ↓ [89] | | | | | | |

Note: ↑ – increase in numbers; ↓ – decrease in numbers.
In the study of multiple clerosis (MS), changes in gut microbiota were evaluated, Sjögren's disease (SD) – oral cavity, psoriasis (P) – skin.
Примечание: ↑ – повышение численности; ↓ – снижение численности.
При изучении рассеянного склероза (РС) оценивались изменения микробиоты кишечника, болезни Шёгрена (БШ) – ротовой полости, псориаза (П) – кожи.

demonstrated [73]. Moreover, according to some data, the gut microbiota may influence myelination regulation in the CNS [74].

In experiments on transgenic mice and mice with autoimmune encephalomyelitis induced by myelin oligodendrocyte glycoprotein, transplantation of microbiota from MS patients increased the frequency of disease development and worsened its symptoms compared to transplantation of gut microbiota from healthy donors [75, 76]. In MS patients, the microbiota from healthy donors alleviated disease symptoms by reducing microglial activation and restoring BBB permeability [13] as well as normalising the level of brain-derived neurotrophic factor in serum and improving gait parameters [14].

Similarly, the use of probiotics influenced the course of the disease, for example, in an animal model of autoimmune encephalomyelitis, the administration of the *Escherichia coli* strain Nissle 1917 led to reduced migration of autoreactive $CD4^+$ T cells into the CNS and restoration of intestinal permeability [18]. *Lactobacillus paracasei* DSM 13434, *Lactobacillus plantarum* DSM 15312, and *Lactobacillus plantarum* DSM 15313 strains promoted the induction of regulatory T cells. Interestingly, when administered individually, they only exhibited a prophylactic effect, while combined administration had a pronounced therapeutic effect [19]. A similar synergistic effect was observed with the combined use of *Lactobacillus plantarum* A7 and *Bifidobacterium animalis* [20].

Thus, complex interactions between microorganisms can sometimes lead to new therapeutic effects, both favourable and unfavourable, and we should consider this when selecting probiotic therapy. In two independent studies, the therapeutic application of *Lactobacillus reuteri* bacteria was shown to be associated with alleviation and exacerbation of symptoms of autoimmune encephalomyelitis [21, 77]. This variability may be explained by the peculiarities of interaction with other commensals of the gut microbiota, as well as by the expression of peptides by *L. reuteri* that potentially mimic myelin oligodendrocyte glycoprotein [78].

## THE ROLE OF SKIN MICROBIOTA IN THE DEVELOPMENT OF PSORIASIS

Psoriasis is a chronic immune-mediated multifactorial disease affecting the skin. Epidemiological data indicate that 2-3% of the global population suffers from psoriasis, making it a socially significant illness that drastically impairs the patients' quality of life and, in some cases, leads to their social isolation and stigmatisation [79, 80].

The immune system plays a pivotal role in psoriasis development: in healthy skin, T cells and dendritic cells present in low numbers and contribute to the protection against pathogens. In psoriasis, however, there is an escalation in activated T cells and dendritic cells in the skin. They release pro-inflammatory cytokines, initiating a cascade of reactions underlying psoriasis symptoms, such as keratinocyte hyperproliferation, aberrant differentiation, and angiogenesis [81].

For example, IL-6 inhibits T regulatory cell function, exacerbating inflammation [82, 83]. On the other hand, the activation of T helper 17 cells stimulates IL-17 and IL-22 synthesis, fostering keratinocyte proliferation [84, 85]. These interleukins also facilitate the recruitment of monocytes from the bloodstream, which under the influence of pro-inflammatory cytokines differentiate into macrophages and dendritic cells and start producing pro-inflammatory cytokines, including tumour necrosis factor-alpha [81].

Despite the array of treatment approaches available for psoriasis and the potential for achieving sustained remission in many cases, the condition remains incurable. Mild psoriasis can currently be treated topically via

glucocorticoids, vitamin D, or phototherapy, while severe cases may necessitate systemic therapies like retinoids, methotrexate, cyclosporine, and monoclonal antibody drugs. Nonetheless, patient responses to the chosen treatments can be variable, and prolonged systemic therapy is often associated with adverse effects, prompting exploration into novel psoriasis treatment strategies [30].

In recent years, increasing evidence has emerged regarding the involvement of the microbiome in the pathogenesis of psoriasis [10, 11]. The systemic nature of the disease is associated with changes in the microbiota of various body sites, including the skin [86–91] (see table).

Notably, for some taxa in psoriasis, particularly the genus *Staphylococcus*, different studies have shown both increases [86, 88] and decreases [87, 90] in abundance. This phenomenon can be attributed to variations in methodological approaches in research. It is known that the microbiota of unaffected skin in psoriasis patients differs from that of affected areas, but it also differs from the skin microbiota of healthy volunteers [92, 93]. For instance, studies by Z. Gao et al. [86] and A. Boix-Amorós et al. [88] analysed the characteristics of microbiota in affected and unaffected skin in psoriasis, as well as the skin microbiota of healthy volunteers while in the study by A. Fahlen et al. [87] samples of unaffected skin in psoriasis patients were not analysed, and in the study by M. Assarsson et al. [90], there was no healthy volunteer group. The choice of anatomical area for sampling also influences the research outcome, which may be attributed to the physiological differences in the skin across body regions [94, 95]. Finally, the method of sample collection (biopsy or skin swabs) can also impact the research outcome, which needs to be considered when interpreting and discussing the obtained results [86–88, 90, 92].

In experiments on the imiquimod-induced psoriasis model in mice, as well as in clinical trials, reduction of psoriasis-like inflammation in animals and symptoms of psoriasis in patients receiving antibiotics and probiotics have been repeatedly demonstrated [15, 16, 23–25, 96]. However, while the effect of probiotics on the gut microbiota in psoriasis has been extensively discussed in the literature, there is little data on the modulation of skin microbiota in psoriasis through local application of agents [97, 98].

It was demonstrated that the skin microbiota in psoriasis changes in response to biological therapy: for example, treatment with ustekinumab, an inhibitor of IL-12 and IL-23, led to an increase in the abundance of *Acinetobacter* family and a decrease in the class *Bacilli* and order *Gemellales* bacteria on the trunk skin, as well as an increase in the abundance of bacteria from the *Bradyrhizobiaceae* family and a decrease in *Staphylococcus* bacteria on the scalp [94]. Following ultraviolet therapy in psoriatic plaque areas and unaffected skin of patients, the abundance of *Pseudomonas* bacteria significantly decreased, while the abundance of *Clostridium* bacteria increased [90]. Additionally, phototherapy markedly reduced the abundance of bacteria from the class *Bacteroidia,* order *Enterobacteriales*, families *Bacteroidaceae*, *Odoribacteraceae*, *Prevotellaceae*, *Enterobacteriaceae*, as well as genera *Bacteroides*, *Odoribacter*, *Prevotella* on the affected skin [92].

The mechanisms by which skin microbiota influences the development of psoriasis are diverse. For instance, the increased abundance of *Streptococcus pyogenes* in psoriasis leads to the increased production of M-protein, capable of activating autoreactive T-cells due to molecular mimicry with 50-kDa type I keratin [99, 100]. Furthermore, interaction with certain commensal microorganisms enables keratinocytes to produce antimicrobial peptides cathelicidins (LL-37), which bind to nucleic acids of apoptotic epithelial cells. Complexes of LL-37 with DNA stimulate the synthesis of type I interferons by plasmacytoid dendritic cells, while complexes with RNA promote the production of tumour necrosis factor-alpha and inducible nitric oxide synthase (iNOS) by myeloid dendritic cells. These cytokines promote the differentiation of T-cells into IL-17 and IL-22-producing Th17 cells, thus playing a key role in the development of psoriasis [11]. The skin microbiota can trigger aberrant immune responses [101] and influence keratinocyte proliferation [102], contributing to psoriasis development.

## THE ROLE OF ORAL MICROBIOTA IN THE DEVELOPMENT OF SJÖGREN'S DISEASE

Sjögren's disease (SD) is a systemic autoimmune disorder primarily affecting the exocrine glands, particularly the salivary and lacrimal glands. When symptoms develop alongside other autoimmune pathologies like systemic lupus erythematosus or rheumatoid arthritis [103], the condition is known as Sjögren's syndrome. SD is one of the most common ADs, with a global prevalence of 0.5–1% [12, 104].

In SD, the infiltration of $CD4^+$ T cells that produce pro-inflammatory cytokines and the production of antinuclear autoantibodies by B cells results in damage to the exocrine glands, leading to symptoms such as xerostomia, dry conjunctivitis, and dysphagia, along with extraglandular manifestations [105]. Besides significantly impairing the quality of life, this condition is associated with the development of lymphoproliferative disorders in patients, particularly non-Hodgkin's lymphoma [103], and like other ADs, the treatment of BS primarily involves immunosuppressive therapy, although new

targeted pathogenetic approaches are currently being developed [105].

It is speculated that immune response dysregulation to commensal microorganism metabolites may predispose individuals to autoimmune reactions in SD [12]. For instance, it has been shown that a peptide from the von Willebrand factor type A domain protein produced by the oral commensal *Capnocytophaga ochracea* may activate T-cells targeting the Sjögren's syndrome A antigen (SS-A), also known as Ro60, due to cross-reactivity [106]. Conversely, disruption of oral cavity homeostasis due to xerostomia may exacerbate dysbiosis further [107]. Studies have demonstrated that the oral microbiota may serve as a therapeutic target in SD [108]. Specifically, low-dose doxycycline treatment normalised the levels of several metabolites associated with oral microbiota dysbiosis in SD patients [17]. More detailed information on changes in oral microbiota in SD [109-114] is provided in the table.

## EXTRACELLULAR VESICLES AS A POTENTIAL TOOL FOR MICROBIOME MODULATION IN AUTOIMMUNE DISEASES

EVs are involved in numerous physiological and pathological processes and participate in intercellular communication. This communication network encompasses not only vesicles produced by human cells but also vesicles from prokaryotic cells of the microbiome, with the latter discussed as a potential modulating tool, and it has been demonstrated that exosomes can influence the composition of the gut microbiota; however, the precise mechanisms of these interactions are not yet fully understood [115]. Despite the intestines being the most extensively studied locus in the context of the relationship between the human microbiome and ADs, modulation of its microbiota through EVs in ADs is currently underrepresented in the literature. Furthermore, most studies investigating the interaction between EVs and the gut microbiota in autoimmune and inflammatory diseases primarily focus on colitis models. In this review, we deliberately examined the less extensively covered relationship between the gut microbiota and MS, aiming to underscore that disruption of microbiota homeostasis extends beyond the affected organ in ADs. However, some findings obtained in colitis models may be extrapolated to gut microbiota modulation in MS and suggest potential directions for further research.

Promising candidates for modulating the gut microbiota are EVs from lactobacilli, which plays a crucial role in maintaining intestinal microbiota homeostasis and possess specific immunomodulatory potential [116–118]. It has been shown that EVs from *Lactobacillus plantarum* Q7 contribute to reducing the abundance of pro-inflammatory *Proteobacteria* and increasing the abundance of anti-inflammatory bacteria such as *Bifidobacteria* and *Muribaculaceae* in the intestine [39].

In recent years, EVs derived from milk have been widely studied. This approach allows for the obtaining of a mixture of vesicles from various beneficial bacteria, including lactobacilli. It has been reported that EVs from milk contribute to an increase in the abundance of bacteria from the genera *Dubosiella*, *Bifidobacterium*, *Lachnoclostridium*, and *Lachnospiraceae* in the gut [40]. Moreover, *in vitro* studies have demonstrated the selective effect of milk exosomes on bacteria; they exhibited no bactericidal activity against gram-positive bacteria such as *Staphylococcus aureus*, *Micrococcus luteus*, and *Enterococcus faecalis*, but demonstrated bacteriostatic effects against gram-negative strains like *Escherichia coli*, *Pseudomonas aeruginosa*, and *Proteus mirabilis*, as well as fungistatic effects against *Candida albicans* [41]. Additionally, milk EVs have been shown to promote the restoration of intestinal barrier integrity in a murine model of dextran sodium sulphate-induced colitis [35]. This phenomenon may be associated with the stimulation of short-chain fatty acid synthesis in the intestine and their esters, particularly butyrate and acetate [40]. Human placental mesenchymal stem cell exosomes were also shown to influence the synthesis of short-chain fatty acids in the gut. In an experiment conducted by L. Yang et al., unlike milk exosomes, they did not significantly affect the synthesis of acetic acid but promoted the synthesis of caprylic, valeric, and isocaproic acids [36].

Regarding the potential modulation of the skin microbiota through EVs, it is important to note that the terms "prebiotics" (non-digestible fermentable compounds that stimulate the growth and activity of beneficial bacteria), "probiotics" (live microorganisms that exert a positive effect on the host organism's health), and "postbiotics" (metabolites of microorganisms that positively affect on the host organism's health) have traditionally been applied in the context of the gut microbiota. However, in recent years, they have also been actively used in the context of the skin microbiota and local application [98, 119–121].

EVs are rich in polyunsaturated fatty acids, thus capable of acting as prebiotics, promoting the growth of lipophilic bacteria, particularly *Cutibacterium* (formerly *Propionibacterium*), whose abundance decreases in psoriasis [122–125]. Such changes in the microbiome are significant in the pathogenesis of psoriasis because these bacteria contribute to the development of an immune response mediated by T-helper 2 cells, and a decrease in their quantity shifts the balance towards a T-helper 1-mediated response associated with autoimmune activity [121].

On the other hand, EVs derived from bacteria, as products of their metabolism, can act as postbiotics, and according to some data, the effectiveness of

bacterial exosomes is comparable to that of live bacteria [37, 38]. Moreover, using EVs for therapy instead of live bacteria may overcome limitations associated with the fact that live bacteria can be weakened or damaged during cultivation or storage. Several studies have demonstrated the beneficial effects of EVs from healthy microbiota (*Lactobacillus plantarum*, *Cutibacterium acnes*, *Staphylococcus epidermidis*) on the skin, including regulation of sebum secretion [126], reduction of pigmentation and wrinkle formation [127], and alleviation of symptoms of atopic dermatitis [128, 129].

Modulation of the oral microbiota remains a challenging task and is often considered in combination with modulation of the gut microbiota. However, certain probiotics have been shown to influence pathogen adhesion, biofilm formation, and maintenance of optimal pH in the oral cavity [130]. The *Lactobacillus acidophilus* LA5 strain was shown to reduce the adhesion of pathogenic microorganisms *Porphyromonas gingivalis* and *Fusobacterium nucleatum*, while *Lactobacillus fermentum* bacteria reduced the adhesion of *Streptococcus mutans* [131, 132]. In turn, *Lactobacillus salivarius* bacteria contribute to increased saliva buffering capacity (the ability of saliva to neutralize acids and alkalis, maintaining optimal pH) [133]. Thus, lactobacilli represent a promising source of EVs for combating both gut dysbiosis and for modulating the oral microbiota, including autoimmune conditions.

Analysis of literature data revealed a certain imbalance in studies of the effects of EVs of eukaryotic and prokaryotic origin. Despite the scientific community recognising the fundamental role of EVs in intercellular communication and maintaining homeostasis, EVs produced by the human microbiome are more often considered in the context of their influence on the microbiome while those produced by human cells are studied concerning the whole organism. At the same time, the interaction of both types of vesicles remains an understudied, yet promising area for the development of new medicinal products.

## CONCLUSION

Recent studies have underscored the significant role of the human microbiome in AD development. While it is still currently unclear whether dysbiosis is a cause or consequence of immune dysregulation, several studies have demonstrated that targeting the microbiome alleviates symptoms of the underlying disease, suggesting it could be an effective therapeutic strategy. As previously shown, EVs exhibit a wide spectrum of therapeutic activity due to their biologically active constituents. Moreover, recent research findings suggest they may also be effective in modulating the microbiota across various human body sites, including in ADs. EVs sourced from diverse origins are capable of fostering the growth of beneficial microbiota while inhibiting pathogen proliferation. Enhanced comprehension of the intricate mechanisms governing the interplay among EVs, the microbiome, and the human immune system is imperative for devising novel strategies for AD therapy.

## AUTHORS CONTRIBUTIONS

Maria A. Peshkova, Alexander A. Korneev, and Polina I. Koteneva contributed to the compilation and analysis of literary sources, drafting the article, compiling the reference list, and preparing the manuscript for publication. Nastasia V. Kosheleva conducted scientific editing of the manuscript, refining its content. Peter S. Timashev curated essential information pertaining to the subject matter and coordinated the finalization of the manuscript. All the authors approved the final version of the article.

## ВКЛАД АВТОРОВ

М.А. Пешкова, А.А. Корнеев и П.И. Котенева участвовали в сборе и анализе литературных источников, написании текста статьи, оформлении списка литературы, подготовке материала для публикации. Н.В. Кошелева провела научное редактирование статьи, доработала текст. П.С. Тимашев отвечал за отбор ключевой информации по тематике, финальную подготовку текста. Все авторы утвердили окончательную версию статьи.

## REFERENCES / ЛИТЕРАТУРА


1. *Guo H., Li L., Liu B., et al.* Inappropriate treatment response to DMARDs: A pathway to difficult-to-treat rheumatoid arthritis. Int Immunopharmacol. 2023 Sep; 122: 110655. https://doi.org/10.1016/J.INTIMP.2023.110655. Epub 2023 Jul 21. PMID: 37481847
2. *Laigle L., Chadli L., Moingeon P.* Biomarker-driven development of new therapies for autoimmune diseases: current status and future promises. Expert Rev Clin Immunol. 2023 Mar; 19(3): 305–314. https://doi.org/10.1080/1744666X.2023.2172404. Epub 2023 Jan 27. PMID: 36680799
3. *Vangoitsenhoven R., Cresci G.A.M.* Role of microbiome and antibiotics in autoimmune diseases. Nutr Clin Pract. 2020 Jun; 35(3): 406–416. https://doi.org/10.1002/NCP.10489. Epub 2020 Apr 22. PMID: 32319703
4. *Rosser E.C., Mauri C.* A clinical update on the significance of the gut microbiota in systemic autoimmunity. J Autoimmun. 2016 Nov; 74: 85–93. https://doi.org/10.1016/J.JAUT.2016.06.009. Epub 2016 Jul 29. PMID: 27481556
5. *López P., De Paz B., Rodríguez-Carrio J., et al.* Th17 responses and natural IgM antibodies are related to gut microbiota composition in systemic lupus erythematosus patients. Sci Rep. 2016 Apr 5; 6: 24072. https://doi.org/10.1038/SREP24072. PMID: 27044888; PMCID: PMC4820712
6. *Needell J.C., Zipris D.* The role of the intestinal microbiome in type 1 diabetes pathogenesis. Curr Diab Rep. 2016 Oct; 16(10): 89. https://doi.org/10.1007/S11892-016-0781-Z. PMID: 27523648
7. *Jangi S., Gandhi R., Cox L.M., et al.* Alterations of the human gut microbiome in multiple sclerosis. Nat Commun. 2016 Jun 28; 7: 12015. https://doi.org/10.1038/NCOMMS12015. PMID: 27352007; PMCID: PMC4931233

8. *Chen J., Wright K., Davis J.M., et al.* An expansion of rare lineage intestinal microbes characterizes rheumatoid arthritis. Genome Med. 2016 Apr 21; 8(1): 43. https://doi.org/10.1186/S13073-016-0299-7. PMID: 27102666; PMCID: PMC4840970
9. *Coit P., Sawalha A.H.* The human microbiome in rheumatic autoimmune diseases: A comprehensive review. Clin Immunol. 2016 Sep; 170: 70–79. https://doi.org/10.1016/J.CLIM.2016.07.026. Epub 2016 Aug 2. PMID: 27493014
10. *Wang W.M., Jin H.Z.* Skin microbiome: an actor in the pathogenesis of psoriasis. Chin Med J (Engl). 2018 Jan 5; 131(1): 95–98. https://doi.org/10.4103/0366-6999.221269. PMID: 29271387; PMCID: PMC5754965
11. *Olejniczak-Staruch I., Ciążyńska M., Sobolewska-Sztychny D., et al.* Alterations of the skin and gut microbiome in psoriasis and psoriatic arthritis. Int J Mol Sci. 2021 Apr 13; 22(8): 3998. https://doi.org/10.3390/ijms22083998. PMID: 33924414; PMCID: PMC8069836
12. *Nikitakis N.G., Papaioannou W., Sakkas L.I., et al.* The autoimmunity–oral microbiome connection. Oral Dis. 2017 Oct; 23(7): 828–839. https://doi.org/10.1111/ODI.12589. Epub 2016 Nov 24. PMID: 27717092
13. *Li K., Wei S., Hu L., et al.* Protection of fecal microbiota transplantation in a mouse model of multiple sclerosis. Mediators Inflamm. 2020 Aug 5; 2020: 2058272. https://doi.org/10.1155/2020/2058272. PMID: 32831634; PMCID: PMC7426773
14. *Engen P.A., Zaferiou A., Rasmussen H., et al.* Single-arm, non-randomized, time series, single-subject study of fecal microbiota transplantation in multiple sclerosis. Front Neurol. 2020 Sep 8; 11: 978. https://doi.org/10.3389/fneur.2020.00978. PMID: 33013647; PMCID: PMC7506051
15. *Vijayashankar M., Raghunath N.* Pustular psoriasis responding to probiotics – a new insight. Our Dermatology Online. 2012; 3: 326–329. https://doi.org/10.7241/OURD.20124.71
16. *Choy C.T., Chan U.K., Siu P.L.K., et al.* A novel E3 probiotics formula restored gut dysbiosis and remodelled gut microbial network and microbiome dysbiosis index (MDI) in Southern Chinese adult psoriasis patients. Int J Mol Sci. 2023 Mar 31; 24(7): 6571. https://doi.org/10.3390/ijms24076571. PMID: 37047542; PMCID: PMC10094986
17. *Herrala M., Turunen S., Hanhineva K., et al.* Low-dose doxycycline treatment normalizes levels of some salivary metabolites associated with oral microbiota in patients with primary Sjögren's syndrome. Metabolites. 2021 Sep 3; 11(9): 595. https://doi.org/10.3390/metabo11090595. PMID: 34564411; PMCID: PMC8470364
18. *Secher T., Kassem S., Benamar M., et al.* Oral administration of the probiotic strain Escherichia coli Nissle 1917 reduces susceptibility to neuroinflammation and repairs experimental autoimmune encephalomyelitis-induced intestinal barrier dysfunction. Front Immunol. 2017 Sep 14; 8: 1096. https://doi.org/10.3389/fimmu.2017.01096. PMID: 28959254; PMCID: PMC5603654
19. *Lavasani S., Dzhambazov B., Nouri M., et al.* A novel probiotic mixture exerts a therapeutic effect on experimental autoimmune encephalomyelitis mediated by IL-10 producing regulatory T cells. PLoS One. 2010 Feb 2; 5(2): e9009. https://doi.org/10.1371/JOURNAL.PONE.0009009. PMID: 20126401; PMCID: PMC2814855
20. *Salehipour Z., Haghmorad D., Sankian M., et al.* Bifidobacterium animalis in combination with human origin of Lactobacillus plantarum ameliorate neuroinflammation in experimental model of multiple sclerosis by altering CD4+ T cell subset balance. Biomed Pharmacother. 2017 Nov; 95: 1535–1548. https://doi.org/10.1016/J.BIOPHA.2017.08.117. Epub 2017 Sep 22. PMID: 28946394
21. *He B., Hoang T.K., Tian X., et al.* Lactobacillus reuteri reduces the severity of experimental autoimmune encephalomyelitis in mice by modulating gut microbiota. Front Immunol. 2019 Mar 7; 10: 385. https://doi.org/10.3389/FIMMU.2019.00385. PMID: 30899262; PMCID: PMC6416370
22. *Zhao Q., Yu J., Zhou H., et al.* Intestinal dysbiosis exacerbates the pathogenesis of psoriasis-like phenotype through changes in fatty acid metabolism. Sig Transduct Target Ther. 2023 Jan 30; 8(1): 40. https://doi.org/10.1038/s41392-022-01219-0. PMID: 36710269; PMCID: PMC9884668
23. *Lu W., Deng Y., Fang Z., et al.* Potential role of probiotics in ameliorating psoriasis by modulating gut microbiota in imiquimod-induced psoriasis-like mice. Nutrients. 2021 Jun 11; 13(6): 2010. https://doi.org/10.3390/NU13062010. PMID: 34207960; PMCID: PMC8230682
24. *Chen Y.H., Wu C.S., Chao Y.H., et al.* Lactobacillus pentosus GMNL-77 inhibits skin lesions in imiquimod-induced psoriasis-like mice. J food drug Anal. 2017 Jul; 25(3): 559–566. https://doi.org/10.1016/J.JFDA.2016.06.003. Epub 2016 Aug 5. PMID: 28911642; PMCID: PMC9328808
25. *Rather I.A., Bajpai V.K., Huh Y.S., et al.* Probiotic lactobacillus sakei proBio-65 extract ameliorates the severity of imiquimod induced psoriasis-like skin inflammation in a mouse model. Front Microbiol. 2018 May 17; 9: 1021. https://doi.org/10.3389/fmicb.2018.01021. PMID: 29867905; PMCID: PMC5968580
26. *Akers J.C., Gonda D., Kim R., et al.* Biogenesis of extracellular vesicles (EV): exosomes, microvesicles, retrovirus-like vesicles, and apoptotic bodies. J Neurooncol. 2013 May; 113(1): 1–11. https://doi.org/10.1007/s11060-013-1084-8. Epub 2013 Mar 2. PMID: 23456661; PMCID: PMC5533094
27. *Zhang J., Buller B.A., Zhang Z.G., et al.* Exosomes derived from bone marrow mesenchymal stromal cells promote remyelination and reduce neuroinflammation in the demyelinating central nervous system. Exp Neurol. 2022 Jan; 347: 113895. https://doi.org/10.1016/J.EXPNEUROL.2021.113895. Epub 2021 Oct 13. PMID: 34653510
28. *Riazifar M., Mohammadi M.R., Pone E.J., et al.* Stem cell-derived exosomes as nanotherapeutics for autoimmune and neurodegenerative disorders. ACS Nano. 2019 Jun 25; 13(6): 6670–6688. https://doi.org/10.1021/acsnano.9b01004. Epub 2019 May 29. PMID: 31117376; PMCID: PMC6880946
29. *Kimura K.* Regulatory T cells in multiple sclerosis. Clin Exp Neuroimmunol. 2020 Aug; 11: 148–155. https://doi.org/10.1111/CEN3.12591
30. *Zhang B., Lai R.C., Sim WK., et al.* Topical application of mesenchymal stem cell exosomes alleviates the imiquimod induced psoriasis-like inflammation. Int J Mol Sci. 2021 Jan 13; 22(2): 720. https://doi.org/10.3390/IJMS22020720. PMID: 33450859; PMCID: PMC7828312
31. *Zhang Y., Yan J., Li Z., et al.* Exosomes derived from human umbilical cord mesenchymal stem cells alleviate psoriasis-like skin inflammation. J Interferon Cytokine Res. 2022 Jan; 42(1): 8–18. https://doi.org/10.1089/JIR.2021.0146. PMID: 35041513
32. *Rodrigues S.C., Cardoso R.M.S., Freire P.C., et al.* Immunomodulatory properties of umbilical cord blood-derived small extracellular vesicles and their therapeutic potential for inflammatory skin disorders. Int J Mol Sci. 2021 Sep 10; 22(18): 9797. https://doi.org/10.3390/IJMS22189797. PMID: 34575956; PMCID: PMC8468428
33. *Xing Y., Li B., He J., et al.* Labial gland mesenchymal stem cell derived exosomes-mediated miRNA-125b attenuates experimental Sjögren's syndrome by targeting PRDM1 and suppressing plasma cells. Front Immunol. 2022 Apr 4; 13: 871096. https://doi.org/10.3389/fimmu.2022.871096. PMID: 35444638; PMCID: PMC9014006

34. *Zhao Q., Bae E.H., Zhang Y., et al.* Inhibitory effects of extracellular vesicles from iPS-cell-derived mesenchymal stem cells on the onset of sialadenitis in Sjögren's syndrome are mediated by immunomodulatory splenocytes and improved by inhibiting miR-125b. Int J Mol Sci. 2023 Mar 9; 24(6): 5258. https://doi.org/10.3390/ijms24065258 PMID: 36982329; PMCID: PMC10049013
35. *Tong L., Zhang S., Liu Q., et al.* Milk-derived extracellular vesicles protect intestinal barrier integrity in the gut-liver axis. Sci Adv. 2023 Apr 14; 9(15): eade5041. https://doi.org/10.1126/SCIADV.ADE5041. Epub 2023 Apr 12. PMID: 37043568; PMCID: PMC10096581
36. *Yang L., Wang T., Zhang X., et al.* Exosomes derived from human placental mesenchymal stem cells ameliorate myocardial infarction via anti-inflammation and restoring gut dysbiosis. BMC Cardiovasc Disord. 2022 Feb 17; 22(1): 61. https://doi.org/10.1186/S12872-022-02508-W. PMID: 35172728; PMCID: PMC8851843
37. *Barros C.P., Guimarães J.T., Esmerino E.A., et al.* Paraprobiotics and postbiotics: concepts and potential applications in dairy products. Curr Opin Food Sci. 2020; 32: 1–8. https://doi.org/10.1016/J.COFS.2019.12.003
38. *González-Lozano E., García-García J., Gálvez J., et al.* Novel horizons in postbiotics: Lactobacillaceae extracellular vesicles and their applications in health and disease. Nutrients. 2022 Dec 13; 14(24): 5296. https://doi.org/10.3390/NU14245296. PMID: 36558455; PMCID: PMC9782203
39. *Hao H., Zhang X., Tong L., et al.* Effect of extracellular vesicles derived from lactobacillus plantarum Q7 on gut microbiota and ulcerative colitis in mice. Front Immunol. 2021 Dec 2; 12: 777147. https://doi.org/10.3389/FIMMU.2021.777147. PMID: 34925349; PMCID: PMC8674835
40. *Du C., Wang K., Zhao Y., et al.* Supplementation with milk-derived extracellular vesicles shapes the gut microbiota and regulates the transcriptomic landscape in experimental colitis. Nutrients. 2022 Apr 26; 14(9): 1808. https://doi.org/10.3390/NU14091808. PMID: 35565775; PMCID: PMC9104790
41. *Shaban A.M., Raslan M., Sharawi Z.W., et al.* Antibacterial, antifungal, and anticancer effects of camel milk exosomes: an in vitro study. Vet Sci. 2023 Feb 6; 10(2): 124. https://doi.org/10.3390/VETSCI10020124. PMID: 36851428; PMCID: PMC9963947
42. *Wajda D.A., Sosnoff J.J.* Cognitive-motor interference in multiple sclerosis: a systematic review of evidence, correlates, and consequences. Biomed Res Int. 2015; 2015: 720856. https://doi.org/10.1155/2015/720856. Epub 2015 Mar 9. PMID: 25839039; PMCID: PMC4369906
43. *Rutsch A., Kantsjö J.B., Ronchi F.* The gut-brain axis: how microbiota and host inflammasome influence brain physiology and pathology. Front Immunol. 2020 Dec 10; 11: 604179. https://doi.org/10.3389/FIMMU.2020.604179. PMID: 33362788; PMCID: PMC7758428
44. *Dyńka D., Kowalcze K., Paziewska A.* The role of ketogenic diet in the treatment of neurological diseases. Nutrients. 2022 Nov 24; 14(23): 5003. https://doi.org/10.3390/NU14235003. PMID: 36501033; PMCID: PMC9739023
45. *Mora P., Chapouly C.* Astrogliosis in multiple sclerosis and neuroinflammation: what role for the notch pathway? Front Immunol. 2023 Oct 23; 14: 1254586. https://doi.org/10.3389/FIMMU.2023.1254586. PMID: 37936690; PMCID: PMC10627009
46. *Schauf M., Chinthapatla H., Dimri S., et al.* Economic burden of multiple sclerosis in the United States: A systematic literature review. J Manag care Spec Pharm. 2023 Dec; 29(12): 1354-1368. https://doi.org/10.18553/JMCP.2023.23039. Epub 2023 Nov 17. PMID: 37976077; PMCID: PMC10776266
47. *Hauser S.L., Cree B.A.C.* Treatment of multiple sclerosis: a review. Am J Med. 2020 Dec; 133(12): 1380-1390.e2. https://doi.org/10.1016/J.AMJMED.2020.05.049. Epub 2020 Jul 17. PMID: 32682869; PMCID: PMC7704606
48. *Baecher-Allan C., Kaskow B.J., Weiner H.L.* Multiple sclerosis: mechanisms and immunotherapy. Neuron. 2018 Feb 21; 97(4): 742–768. https://doi.org/10.1016/J.NEURON.2018.01.021. PMID: 29470968
49. *Prajeeth C.K., Dittrich-Breiholz O., Talbot S.R., et al.* IFN-γ producing Th1 cells induce different transcriptional profiles in microglia and astrocytes. Front Cell Neurosci. 2018 Oct 10; 12: 352. https://doi.org/10.3389/fncel.2018.00352. PMID: 30364000; PMCID: PMC6191492
50. *Chen J., Liu X., Zhong Y.* Interleukin-17A: The Key cytokine in neurodegenerative diseases. Front Aging Neurosci. 2020 Sep 29; 12: 566922. https://doi.org/10.3389/fnagi.2020.566922. PMID: 33132897; PMCID: PMC7550684
51. *Yu A., Duan H., Zhang T., et al.* IL-17A promotes microglial activation and neuroinflammation in mouse models of intracerebral haemorrhage. Mol Immunol. 2016 May; 73: 151–157. https://doi.org/10.1016/J.MOLIMM.2016.04.003. Epub 2016 Apr 22. PMID: 27107665
52. *Huppert J., Closhen D., Croxford A., et al.* Cellular mechanisms of IL-17-induced blood-brain barrier disruption. FASEB J. 2010 Apr; 24(4): 1023–1034. https://doi.org/10.1096/FJ.09-141978. Epub 2009 Nov 25. PMID: 19940258
53. *Alvarez J.I., Cayrol R., Prat A.* Disruption of central nervous system barriers in multiple sclerosis. Biochim Biophys Acta – Mol Basis Dis. 2011 Feb; 1812(2): 252–264. https://doi.org/10.1016/J.BBADIS.2010.06.017. Epub 2010 Jul 7. PMID: 20619340
54. *Fraussen J., de Bock L., Somers V.* B cells and antibodies in progressive multiple sclerosis: Contribution to neurodegeneration and progression. Autoimmun Rev. 2016 Sep; 15(9): 896–899. https://doi.org/10.1016/J.AUTREV.2016.07.008. Epub 2016 Jul 7. PMID: 27396817
55. *Holloman J.P., Axtell R.C., Monson N.L., et al.* The role of B Cells in primary progressive multiple sclerosis. Front Neurol. 2021 Jun 7; 12: 680581. https://doi.org/10.3389/FNEUR.2021.680581. PMID: 34163430; PMCID: PMC8215437
56. *Ochoa-Reparaz J., Magori K., Kasper L.H.* The chicken or the egg dilemma: intestinal dysbiosis in multiple sclerosis. Ann Transl Med. 2017 Mar; 5(6): 145. https://doi.org/10.21037/ATM.2017.01.18. PMID: 28462225; PMCID: PMC5395488
57. *Gandy K.A.O., Zhang J., Nagarkatti P., et al.* The role of gut microbiota in shaping the relapse-remitting and chronic-progressive forms of multiple sclerosis in mouse models. Sci Rep. 2019 May 6; 9(1): 6923. https://doi.org/10.1038/S41598-019-43356-7. PMID: 31061496; PMCID: PMC6502871
58. *Parodi B., Kerlero de Rosbo N.* The gut-brain axis in multiple sclerosis. Is Its dysfunction a pathological trigger or a consequence of the disease? Front Immunol. 2021 Sep 21; 12: 718220. https://doi.org/10.3389/FIMMU.2021.718220. PMID: 34621267; PMCID: PMC8490747
59. *Miyake S., Kim S., Suda W., et al.* Dysbiosis in the gut microbiota of patients with multiple sclerosis, with a striking depletion of species belonging to Clostridia XIVa and IV clusters. PLoS One. 2015 Sep 14; 10(9): e0137429. https://doi.org/10.1371/JOURNAL.PONE.0137429. PMID: 26367776; PMCID: PMC4569432
60. *Yadav M., Ali S., Shrode R.L., et al.* Multiple sclerosis patients have an altered gut mycobiome and increased fungal to bacterial richness. PLoS One. 022 Apr 26; 17(4): e0264556. https://doi.org/10.1371/JOURNAL.PONE.0264556. PMID: 35472144; PMCID: PMC9041819
61. *Chen J., Chia N., Kalari K.R., et al.* Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. Sci

Rep. 2016 Jun 27; 6: 28484. https://doi.org/10.1038/SREP28484. PMID: 27346372; PMCID: PMC4921909
62. *Nouri M., Bredberg A., Weström B., et al.* Intestinal barrier dysfunction develops at the onset of experimental autoimmune encephalomyelitis, and can be induced by adoptive transfer of auto-reactive T cells. PLoS One. 2014 Sep 3; 9(9): e106335. https://doi.org/10.1371/JOURNAL.PONE.0106335. PMID: 25184418; PMCID: PMC4153638
63. *Buscarinu M.C., Cerasoli B., Annibali V., et al.* Altered intestinal permeability in patients with relapsing-remitting multiple sclerosis: A pilot study. Mult Scler. 2017 Mar; 23(3): 442–446. https://doi.org/10.1177/1352458516652498. Epub 2016 Jul 11. PMID: 27270497
64. *Kinashi Y., Hase K.* Partners in leaky gut syndrome: intestinal dysbiosis and autoimmunity. Front Immunol. 2021 Apr 22; 12: 673708. https://doi.org/10.3389/FIMMU.2021.673708. PMID: 33968085; PMCID: PMC8100306
65. *Pellegrino A., Coppola G., Santopaolo F., et al.* Role of Akkermansia in human diseases: from causation to therapeutic properties. Nutrients. 2023 Apr 8; 15(8): 1815. https://doi.org/10.3390/NU15081815. PMID: 37111034; PMCID: PMC10142179
66. *Derrien M., Van Baarlen P., Hooiveld G., et al.* Modulation of mucosal immune response, tolerance, and proliferation in mice colonized by the mucin-degrader Akkermansia muciniphila. Front Microbiol. 2011 Aug 1; 2: 166. https://doi.org/10.3389/FMICB.2011.00166. PMID: 21904534; PMCID: PMC3153965
67. *Wu N., Li X., Ma H., et al.* The role of the gut microbiota and fecal microbiota transplantation in neuroimmune diseases. Front Neurol. 2023 Feb 1; 14: 1108738. https://doi.org/10.3389/FNEUR.2023.1108738. PMID: 36816570; PMCID: PMC9929158
68. *Braniste V., Al-Asmakh M., Kowal C., et al.* The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014 Nov 19; 6(263): 263ra158. https://doi.org/10.1126/SCITRANSLMED.3009759. PMID: 25411471; PMCID: PMC4396848
69. *Venkatesh M., Mukherjee S., Wang H., et al.* Symbiotic bacterial metabolites regulate gastrointestinal barrier function via the xenobiotic sensor PXR and toll-like receptor 4. Immunity. 2014 Aug 21; 41(2): 296–310. https://doi.org/10.1016/J.IMMUNI.2014.06.014. Epub 2014 Jul 24. PMID: 25065623; PMCID: PMC4142105
70. *Scott S.A., Fu J., Chang P.V.* Microbial tryptophan metabolites regulate gut barrier function via the aryl hydrocarbon receptor. Proc Natl Acad Sci USA. 2020 Aug 11; 117(32): 19376–19387. https://doi.org/10.1073/pnas.2000047117. Epub 2020 Jul 27. PMID: 32719140; PMCID: PMC7431026
71. *Singh R., Chandrashekharappa S., Bodduluri S.R., et al.* Enhancement of the gut barrier integrity by a microbial metabolite through the Nrf2 pathway. Nat Commun. 2019 Jan 9; 10(1): 89. https://doi.org/10.1038/S41467-018-07859-7. PMID: 30626868; PMCID: PMC6327034
72. *Rothhammer V., Mascanfroni I.D., Bunse L., et al.* Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and CNS inflammation via the aryl hydrocarbon receptor. Nat Med. 2016 Jun; 22(6): 586–597. https://doi.org/10.1038/NM.4106. Epub 2016 May 9. PMID: 27158906; PMCID: PMC4899206
73. *Ochoa-Repáraz J., Mielcarz D.W., Wang Y., et al.* A polysaccharide from the human commensal Bacteroides fragilis protects against CNS demyelinating disease. Mucosal Immunol. 2010 Sep; 3(5): 487–495. https://doi.org/10.1038/MI.2010.29. Epub 2010 Jun 9. PMID: 20531465
74. *Hoban A.E., Stilling R.M., Ryan F.J., et al.* Regulation of prefrontal cortex myelination by the microbiota. Transl Psychiatry. 2016 Apr 5; 6(4): e774. https://doi.org/10.1038/TP.2016.42. PMID: 27045844; PMCID: PMC4872400
75. *Berer K., Gerdes L.A., Cekanaviciute E., et al.* Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proc Natl Acad Sci U S A. 2017 Oct 3; 114(40): 10719–10724. https://doi.org/10.1073/pnas.1711233114. Epub 2017 Sep 11. PMID: 28893994; PMCID: PMC5635914
76. *Cekanaviciute E., Yoo B.B., Runia T.F., et al.* Gut bacteria from multiple sclerosis patients modulate human T cells and exacerbate symptoms in mouse models. Proc Natl Acad Sci USA. 2017 Oct 3; 114(40): 10713–10718. https://doi.org/10.1073/pnas.1711235114. Epub 2017 Sep 11. PMID: 28893978; PMCID: PMC5635915
77. *Montgomery T.L., Künstner A., Kennedy J.J., et al.* Interactions between host genetics and gut microbiota determine susceptibility to CNS autoimmunity. Proc Natl Acad Sci U S A. 2020 Nov 3; 117(44): 27516–27527. https://doi.org/10.1073/pnas.2002817117. Epub 2020 Oct 19. PMID: 33077601; PMCID: PMC7959502
78. *Miyauchi E., Kim S.W., Suda W., et al.* Gut microorganisms act together to exacerbate inflammation in spinal cords. Nature. 2020 Sep; 585(7823): 102–106. https://doi.org/10.1038/S41586-020-2634-9. Epub 2020 Aug 26. PMID: 32848245
79. *Zhang H., Yang Z., Tang K., et al.* Stigmatization in patients with psoriasis: a mini review. Front Immunol. 2021 Nov 15; 12: 715839. https://doi.org/10.3389/FIMMU.2021.715839. PMID: 34867945; PMCID: PMC8634029
80. *Jankowiak B., Krajewska-Kułak E., Jakoniuk M., et al.* Stigmatization among patients with plaque psoriasis. J Clin Med. 2023 Oct 9; 12(19): 6425. https://doi.org/10.3390/JCM12196425. PMID: 37835068; PMCID: PMC10573936
81. *Zhou X., Chen Y., Cui L., et al.* Advances in the pathogenesis of psoriasis: from keratinocyte perspective. Cell Death Dis. 2022 Jan 24; 13(1): 81. https://doi.org/10.1038/S41419-022-04523-3. PMID: 35075118; PMCID: PMC8786887
82. *Goodman W.A., Levine A.D., Massari J.V., et al.* IL-6 signaling in psoriasis prevents immune suppression by regulatory T cells. J Immunol. 2009 Sep 1; 183(5): 3170–3176. https://doi.org/10.4049/JIMMUNOL.0803721. Epub 2009 Jul 31. PMID: 19648274; PMCID: PMC2903207
83. *Yang L., Li B., Dang E., et al.* Impaired function of regulatory T cells in patients with psoriasis is mediated by phosphorylation of STAT3. J Dermatol Sci. 2016 Feb; 81(2): 85–92. https://doi.org/10.1016/J.JDERMSCI.2015.11.007. Epub 2015 Nov 17. PMID: 26627723
84. *Harris T.J., Grosso J.F., Yen H.-R., et al.* Cutting edge: An in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity. J Immunol. 2007 Oct 1; 179(7): 4313–4317. https://doi.org/10.4049/JIMMUNOL.179.7.4313. PMID: 17878325
85. *Chen Z., Laurence A., Kanno Y., et al.* Selective regulatory function of Socs3 in the formation of IL-17-secreting T cells. Proc Natl Acad Sci USA. 2006 May 23; 103(21): 8137–8142. https://doi.org/ 10.1073/PNAS.0600666103. Epub 2006 May 12. PMID: 16698929; PMCID: PMC1459629
86. *Gao Z., Tseng C.H., Strober B.E., et al.* Substantial alterations of the cutaneous bacterial biota in psoriatic lesions. PLoS One. 2008 Jul 23; 3(7): e2719. https://doi.org/10.1371/JOURNAL.PONE.0002719. PMID: 18648509; PMCID: PMC2447873
87. *Fahlén A., Engstrand L., Baker B.S., et al.* Comparison of bacterial microbiota in skin biopsies from normal and psoriatic skin. Arch Dermatol Res. 2012 Jan; 304(1): 15–22. https://doi.org/10.1007/S00403-011-1189-X. Epub 2011 Nov 8. PMID: 22065152
88. *Boix-Amorós A., Badri M.H., Manasson J., et al.* Alterations in the cutaneous microbiome of patients with psoriasis and psoriatic

arthritis reveal similarities between non-lesional and lesional skin. Ann Rheum Dis. 2023 Apr; 82(4): 507–514. https://doi.org/10.1136/ARD-2022-223389. Epub 2022 Dec 12. PMID: 36600182

89. *Assarsson M., Söderman J., Dienus O., et al.* Significant differences in the bacterial microbiome of the pharynx and skin in patients with psoriasis compared with healthy controls. Acta Derm Venereol. 2020 Sep 30; 100(16): adv00273. https://doi.org/10.2340/00015555-3619. PMID: 32852562; PMCID: PMC9234991
90. *Assarsson M., Duvetorp A., Dienus O., et al.* Significant changes in the skin microbiome in patients with chronic plaque psoriasis after treatment with narrowband ultraviolet B. Acta Derm Venereol. 2018 Apr 16; 98(4): 428–436. https://doi.org/10.2340/00015555-2859. PMID: 29199351
91. *Alekseyenko A.V., Perez-Perez G.I., Souza A. De, et al.* Community differentiation of the cutaneous microbiota in psoriasis. Microbiome. 2013 Dec 23; 1(1): 31. https://doi.org/10.1186/2049-2618-1-31. PMID: 24451201; PMCID: PMC4177411
92. *Rungjang A., Meephansan J., Payungporn S., et al.* Skin microbiota profiles from tape stripping and skin biopsy samples of patients with psoriasis treated with narrowband ultraviolet B. Clin Cosmet Investig Dermatol. 2022 Aug 30; 15: 1767–1778. https://doi.org/10.2147/CCID.S374871. PMID: 36065340; PMCID: PMC9440725
93. *Aslan Kayıran M., Sahin E., Koçoğlu E., et al.* Is cutaneous microbiota a player in disease pathogenesis? Comparison of cutaneous microbiota in psoriasis and seborrheic dermatitis with scalp involvement. Indian J Dermatol Venereol Leprol. 2022 Nov-Dec; 88(6): 738–748. https://doi.org/10.25259/IJDVL_323_21. PMID: 35389020
94. *Loesche M.A., Farahi K., Capone K., et al.* Longitudinal study of the psoriasis-associated skin microbiome during therapy with Ustekinumab in a randomized phase 3b clinical trial. J Invest Dermatol. 2018 Sep; 138(9): 1973–1981. https://doi.org/10.1016/j.jid.2018.03.1501. Epub 2018 Mar 17. PMID: 29559344
95. *Grice E.A., Kong H.H., Conlan S., et al.* Topographical and temporal diversity of the human skin microbiome. Science. 2009 May 29; 324(5931): 1190–1192. https://doi.org/10.1126/SCIENCE.1171700. PMID: 19478181; PMCID: PMC2805064
96. *Zákostelská Z., Málková J., Klimešová K., et al.* Intestinal microbiota promotes psoriasis-like skin inflammation by enhancing Th17 response. PLoS One. 2016 Jul 19; 11(7): e0159539. https://doi.org/10.1371/JOURNAL.PONE.0159539. PMID: 27434104; PMCID: PMC4951142
97. *França K.* Topical probiotics in dermatological therapy and skincare: a concise review. Dermatol Ther (Heidelb). 2021 Feb; 11(1): 71–77. https://doi.org/10.1007/S13555-020-00476-7. Epub 2020 Dec 19. PMID: 33340341; PMCID: PMC7859136
98. *Habeebuddin M., Karnati R.K., Shiroorkar P.N., et al.* Topical probiotics: more than a skin deep. Pharmaceutics. 2022 Mar 3; 14(3): 557. https://doi.org/10.3390/PHARMACEUTICS14030557. PMID: 35335933; PMCID: PMC8955881
99. *Leung D.Y.M., Travers J.B., Giorno R., et al.* Evidence for a streptococcal superantigen-driven process in acute guttate psoriasis. J Clin Invest. 1995 Nov; 96(5): 2106–2112. https://doi.org/10.1172/JCI118263. PMID: 7593594; PMCID: PMC185858
100. *Valdimarsson H., Baker B.S., Jónsdóttir I., et al.* Psoriasis: a T-cell-mediated autoimmune disease induced by streptococcal superantigens? Immunol Today. 1995 Mar; 16(3): 145–149. https://doi.org/10.1016/0167-5699(95)80132-4. PMID: 7718088
101. *Rendon A., Schäkel K.* Psoriasis pathogenesis and treatment. Int J Mol Sci. 2019 Mar 23; 20(6): 1475. https://doi.org/10.3390/ijms20061475. PMID: 30909615; PMCID: PMC6471628
102. *Hsu D.K., Fung M.A., Chen H.-L.* Role of skin and gut microbiota in the pathogenesis of psoriasis, an inflammatory skin disease. Med Microecol. 2020 June; 4: 100016. https://doi.org/10.1016/j.medmic.2020.100016
103. *Kim H., Cho S.K., Kim H.W., et al.* The prevalence of Sjögren's syndrome in rheumatoid arthritis patients and their clinical features. J Korean Med Sci. 2020 Nov 23; 35(45): e369. https://doi.org/10.3346/JKMS.2020.35.E369. PMID: 33230982; PMCID: PMC7683240
104. *Xu J., Chen C., Yin J., et al.* Lactate-induced mtDNA accumulation activates cGAS-STING signaling and the inflammatory response in Sjögren's syndrome. Int J Med Sci. 2023 Aug 15; 20(10): 1256–1271. https://doi.org/10.7150/IJMS.83801. PMID: 37786436; PMCID: PMC10542019
105. *Zhan Q., Zhang J., Lin Y., et al.* Pathogenesis and treatment of Sjögren's syndrome: Review and update. Front Immunol. 2023 Feb 2; 14: 1127417. https://doi.org/10.3389/fimmu.2023.1127417. PMID: 36817420; PMCID: PMC9932901
106. *Szymula A., Rosenthal J., Szczerba B.M., et al.* T cell epitope mimicry between Sjögren's syndrome Antigen A (SSA)/Ro60 and oral, gut, skin and vaginal bacteria. Clin Immunol. 2014 May-Jun; 152(1–2): 1–9. https://doi.org/10.1016/J.CLIM.2014.02.004. Epub 2014 Feb 19. PMID: 24576620; PMCID: PMC4004658
107. *Bellando-Randone S., Russo E., Venerito V., et al.* Exploring the oral microbiome in rheumatic diseases, state of art and future prospective in personalized medicine with an AI approach. J Pers Med. 2021 Jun 30; 11(7): 625. https://doi.org/10.3390/JPM11070625. PMID: 34209167; PMCID: PMC8306274
108. *Lee J., Alam J., Choi E., et al.* Association of a dysbiotic oral microbiota with the development of focal lymphocytic sialadenitis in IκB-ζ-deficient mice. NPJ Biofilms Microbiomes. 2020 Oct 30; 6(1): 49. https://doi.org/10.1038/S41522-020-00158-4. PMID: 33127905; PMCID: PMC7599236
109. *van der Meulen T.A., Harmsen H.J.M., Bootsma H., et al.* Dysbiosis of the buccal mucosa microbiome in primary Sjögren's syndrome patients. Rheumatology (Oxford). 2018 Dec 1; 57(12): 2225–2234. https://doi.org/10.1093/RHEUMATOLOGY/KEY215. PMID: 30060225
110. *Rusthen S., Kristoffersen A.K., Young A., et al.* Dysbiotic salivary microbiota in dry mouth and primary Sjögren's syndrome patients. PLoS One. 2019 Jun 18; 14(6): e0218319. https://doi.org/10.1371/JOURNAL.PONE.0218319. PMID: 31211815; PMCID: PMC6581286
111. *Zhou Z., Ling G., Ding N., et al.* Molecular analysis of oral microflora in patients with primary Sjögren's syndrome by using high-throughput sequencing. PeerJ. 2018 Sep 28; 6: e5649. https://doi.org/10.7717/PEERJ.5649. PMID: 30280027; PMCID: PMC6166617
112. *Siddiqui H., Chen T., Aliko A., et al.* Microbiological and bioinformatics analysis of primary Sjögren's syndrome patients with normal salivation. J Oral Microbiol. 2016 Oct 20; 8: 31119. https://doi.org/10.3402/JOM.V8.31119. PMID: 27770517; PMCID: PMC5075221
113. *Wang X., Pang K., Wang J., et al.* Microbiota dysbiosis in primary Sjögren's syndrome and the ameliorative effect of hydroxychloroquine. Cell Rep. 2022 Sep 13; 40(11): 111352. https://doi.org/10.1016/J.CELREP.2022.111352. PMID: 36103827
114. *Alam J., Lee A., Lee J., et al.* Dysbiotic oral microbiota and infected salivary glands in Sjögren's syndrome. PLoS One. 2020 Mar 24; 15(3): e0230667. https://doi.org/10.1371/JOURNAL.PONE.0230667. PMID: 32208441; PMCID: PMC7092996

115. *Zhou F., Paz H.A., Sadri M., et al.* Nutrient Sensing, nutrition, and metabolism: dietary bovine milk exosomes elicit changes in bacterial communities in C57BL/6 mice. Am J Physiol – Gastrointest Liver Physiol. 2019 Nov 1; 317(5): G618–G624. https://doi.org/10.1152/AJPGI.00160.2019. Epub 2019 Sep 11. PMID: 31509432; PMCID: PMC6879888
116. *Rastogi S., Singh A.* Gut microbiome and human health: exploring how the probiotic genus Lactobacillus modulate immune responses. Front Pharmacol. 2022 Oct 24; 13: 1042189. https://doi.org/10.3389/fphar.2022.1042189. PMID: 36353491; PMCID: PMC9638459
117. *Walter J.* Ecological role of lactobacilli in the gastrointestinal tract: implications for fundamental and biomedical research. Appl Environ Microbiol. 2008 Aug; 74(16): 4985–4996. https://doi.org/10.1128/AEM.00753-08. Epub 2008 Jun 6. PMID: 18539818; PMCID: PMC2519286
118. *Dempsey E., Corr S.C.* Lactobacillus spp. for gastrointestinal health: current and future perspectives. Front Immunol. 2022 Apr 6; 13: 840245. https://doi.org/10.3389/FIMMU.2022.840245. PMID: 35464397; PMCID: PMC9019120
119. *De Almeida C.V., Antiga E., Lulli M.* Oral and topical probiotics and postbiotics in skincare and dermatological therapy: a concise review. Microorganisms. 2023 May 27; 11(6): 1420. https://doi.org/10.3390/MICROORGANISMS11061420. PMID: 37374920; PMCID: PMC10301930
120. *Gelmetti C., Rigoni C., Cantù A.M., et al.* Topical prebiotics/postbiotics and PRURISCORE validation in atopic dermatitis. International study of 396 patients. J Dermatolog Treat. 2023 Dec; 34(1): 2131703. https://doi.org/10.1080/09546634.2022.2131703. Epub 2022 Oct 17. PMID: 36205596
121. *Knackstedt R., Knackstedt T., Gatherwright J.* The role of topical probiotics in skin conditions: A systematic review of animal and human studies and implications for future therapies. Exp Dermatol. 2020 Jan; 29(1): 15–21. https://doi.org/10.1111/EXD.14032. Epub 2019 Sep 18. PMID: 31494971
122. *Hussey G.S., Molina C.P., Cramer M.C., et al.* Lipidomics and RNA sequencing reveal a novel subpopulation of nanovesicle within extracellular matrix biomaterials. Sci Adv. 2020 Mar 20; 6(12): eaay4361. https://doi.org/10.1126/SCIADV.AAY4361. PMID: 32219161; PMCID: PMC7083606
123. *Manzaneque-López M.C., Sánchez-López C.M., Pérez-Bermúdez P., et al.* Dietary-derived exosome-like nanoparticles as bacterial modulators: beyond microRNAs. Nutrients. 2023 Mar 3; 15(5): 1265. https://doi.org/10.3390/NU15051265. PMID: 36904264; PMCID: PMC10005434
124. *Skowron K., Bauza-Kaszewska J., Kraszewska Z., et al.* Human skin microbiome: impact of intrinsic and extrinsic factors on skin microbiota. Microorganisms. 2021 Mar 5; 9(3): 543. https://doi.org/10.3390/MICROORGANISMS9030543. PMID: 33808031; PMCID: PMC7998121
125. *Quan C., Chen X.Y., Li X., et al.* Psoriatic lesions are characterized by higher bacterial load and imbalance between Cutibacterium and Corynebacterium. J Am Acad Dermatol. 2020 Apr; 82(4): 955–961. https://doi.org/10.1016/J.JAAD.2019.06.024. Epub 2019 Jun 19. PMID: 31228520
126. *Cros M.P., Mir-Pedrol J., Toloza L., et al.* New insights into the role of Cutibacterium acnes-derived extracellular vesicles in inflammatory skin disorders. Sci Rep. 2023 Sep 25; 13(1): 16058. https:// 10.1038/S41598-023-43354-W. PMID: 37749255; PMCID: PMC10520063
127. *Jo C.S., Myung C.H., Yoon Y.C., et al.* The effect of lactobacillus plantarum extracellular vesicles from Korean women in their 20s on skin aging. Curr Issues Mol Biol. 2022 Jan 21;44(2):526–540. https://doi.org/10.3390/CIMB44020036. PMID: 35723322; PMCID: PMC8928950
128. *Zhou H., Tan X., Chen G., et al.* Extracellular vesicles of commensal skin microbiota alleviate cutaneous inflammation in atopic dermatitis mouse model by re-establishing skin homeostasis. J Invest Dermatol. 2023 Mar 11: S0022-202X(23)00169-0. https://doi.org/10.1016/J.JID.2023.02.023. Epub ahead of print. PMID: 36907322
129. *Kim M.H., Choi S.J., Choi H., et al.* Lactobacillus plantarum-derived extracellular vesicles protect atopic dermatitis induced by Staphylococcus aureus-derived extracellular vesicles. Allergy Asthma Immunol Res. 2018 Sep; 10(5): 516–532. https://doi.org/10.4168/AAIR.2018.10.5.516. PMID: 30088371; PMCID: PMC6082821
130. *Rebelo M.B., Oliveira C.S., Tavaria F.K.* Novel strategies for preventing dysbiosis in the oral cavity. Front Biosci. 2023 Oct 16; 15(4): 23. https://doi.org/10.31083/j.fbe1504023. PMID: 38163934
131. *Zhang Y., Ding Y., Guo Q.* Probiotic species in the management of periodontal diseases: an overview. Front Cell Infect Microbiol. 2022 Mar 25; 12: 806463. https://doi.org/10.3389/FCIMB.2022.806463. PMID: 35402306; PMCID: PMC8990095
132. *Bizzini B., Pizzo G., Scapagnini G., et al.* Probiotics and oral health. Curr Pharm Des. 2012; 18(34): 5522–5531. https://doi.org/10.2174/138161212803307473. PMID: 22632388
133. *Abikshyeet P., Mishra P., Bhuyan L., et al.* Probiotics: dawn of a new era in dental caries management. J Pharm Bioallied Sci. 2022 Jul; 14(Suppl 1): S34–S38. https://doi.org/10.4103/JPBS.JPBS_801_21. Epub 2022 Jul 13. PMID: 36110745; PMCID: PMC9469361

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