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REVIEW

Synergistic Microbiome-Peptidome Therapeutics: Exploring *Lactobacillus reuteri* DSMZ 17648 and Stem Cell-Derived Peptides for Immunomodulation and Tissue Repair Across Diseases

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ABSTRACT

Chronic inflammatory and degenerative disorders are driven by interconnected immune dysregulation, metabolic instability, epithelial barrier disruption, and impaired tissue repair, limiting the durability of conventional single-target therapies. The global rise in chronic inflammatory, metabolic, and age-related degenerative diseases underscores an urgent need for multi-dimensional therapeutic strategies that move beyond isolated molecular targets. Despite rapid advances in microbiome science and regenerative medicine, these fields have largely evolved in parallel, with limited integration at the translational level. Emerging evidence identifies the gut microbiome as a central regulator of systemic immunometabolic homeostasis through microbial metabolites, barrier integrity modulation, and immune-cell education. In parallel, mesenchymal stem cell (MSC)–derived peptides, key components of the MSC secretome, function as potent cell-free mediators of immunomodulation, angiogenesis, cytoprotection, and extracellular matrix remodeling. This review advances the concept of a microbiome–peptidome therapeutic axis in which microbiome conditioning enhances the permissiveness of tissues to regenerative peptide signaling. Lactobacillus reuteri DSMZ 17648 is highlighted as a strain-specific probiotic capable of pathogen co-aggregation, ecological modulation, and anti-inflammatory microenvironment stabilization, while MSC-derived peptides act as downstream paracrine effectors driving tissue repair. Integrating mechanistic insights with disease-oriented evidence across gastrointestinal, metabolic, neuroinflammatory, and fibrotic conditions, we propose that upstream microbiome stabilization may potentiate peptide-mediated regeneration. However, translational challenges including microbiome heterogeneity, peptide standardization,

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regulatory complexity, and limited combination trials must be addressed. Coordinated, biomarker-guided clinical studies are required to validate this multi-tier therapeutic paradigm.

Keywords: Barrier dysfunction and tissue repair, Immunometabolic regulation, *Lactobacillus reuteri* DSMZ 17648, Microbiome-peptidome axis, Mesenchymal stem cell secretome, Regenerative immunotherapy

1. Introduction

Chronic inflammatory and degenerative disorders remain a major global health burden despite advances in molecular and biologic therapies [1, 2]. Current single-target approaches often fail to achieve sustained clinical benefit because disease pathogenesis is multifactorial, involving immune dysregulation, metabolic imbalance, epithelial barrier dysfunction, and impaired tissue repair [3–5]. Increasing evidence identifies the gut microbiome as a key regulator of systemic immunometabolic homeostasis. Dysbiosis disrupts barrier integrity and immune balance, promotes chronic inflammation, and reduces regenerative capacity [6–8]. Therefore, microbiome-directed strategies represent a biologically rational approach to restoring upstream immune and metabolic stability to support tissue repair [9].

Concurrently, mesenchymal stem cell (MSC) derived peptides, key components of the MSC secretome, have emerged as promising cell-free mediators of tissue repair [10]. These bioactive factors exert immunomodulatory and pro-regenerative effects through paracrine signaling while offering practical advantages over cell-based therapies, including improved safety and regulatory feasibility [11–13]. However, their therapeutic efficacy is highly dependent on the inflammatory and metabolic status of the target tissue, which is influenced by systemic immune balance and microbiota-derived signals [14].

Lactobacillus reuteri DSMZ 17648 is a strain-specific probiotic with documented immunomodulatory and microbiome-stabilizing properties [15]. Rather than acting as a direct regenerative agent, it influences host physiology by restoring microbial ecology, supporting epithelial barrier integrity, and reducing pro-inflammatory signaling [16]. Such upstream microenvironment conditioning may enhance tissue responsiveness to regenerative stimuli. In parallel, MSC-derived peptides function as downstream repair effectors through paracrine immunomodulatory signaling [17].

Despite growing evidence supporting probiotics and MSC-secretome therapies independently, their integration has received limited mechanistic and translational attention. The potential for microbiome conditioning to prime tissues for peptide-mediated regeneration remains insufficiently defined. Critical questions regarding therapeutic sequencing, disease specificity, and molecular interplay therefore warrant systematic exploration [18, 19].

Despite growing evidence supporting probiotics and MSC-secretome therapies independently, these approaches are predominantly investigated in isolation, and an integrated mechanistic framework remains insufficiently defined. Therefore, this review integrates current knowledge on *L. reuteri* DSMZ 17648 and MSC-derived peptide mediated immunoregulation to define a coherent microbiome-peptidome therapeutic framework. The analysis examines how persistent immune activation may limit regenerative responsiveness and evaluates whether microbiome conditioning can enhance peptide-driven repair across inflammatory and degenerative diseases. By combining mechanistic insights with disease-oriented and translational perspectives, key research priorities and clinical considerations for implementing this integrated therapeutic strategy are identified.

This narrative review synthesizes current peer-reviewed literature relevant to microbiome modulation, MSC-derived secretome biology, immunometabolism, and regenerative disease mechanisms. Emphasis was placed on recent mechanistic and translational studies to support the proposed microbiome-peptidome framework.

2. Biological basis of the microbiome-peptidome axis

Microbiome-peptide axis may be seen as a combined system, in which the ecology of microorganisms and their metabolites together regulate host defense tone, tissues of the microenvironment as well as the response level to regenerative signal peptides [20]. At the intestinal interface, commensal microflora control immune homeostasis by modulating inflammation/mucosal antigen exposure, barrier function and education of immune cell functions that favor systemic not chronic immune responses [21]. One primary mechanistic pathway is through microbiota-derived metabolites that serve as critical signaling molecules which program the innate

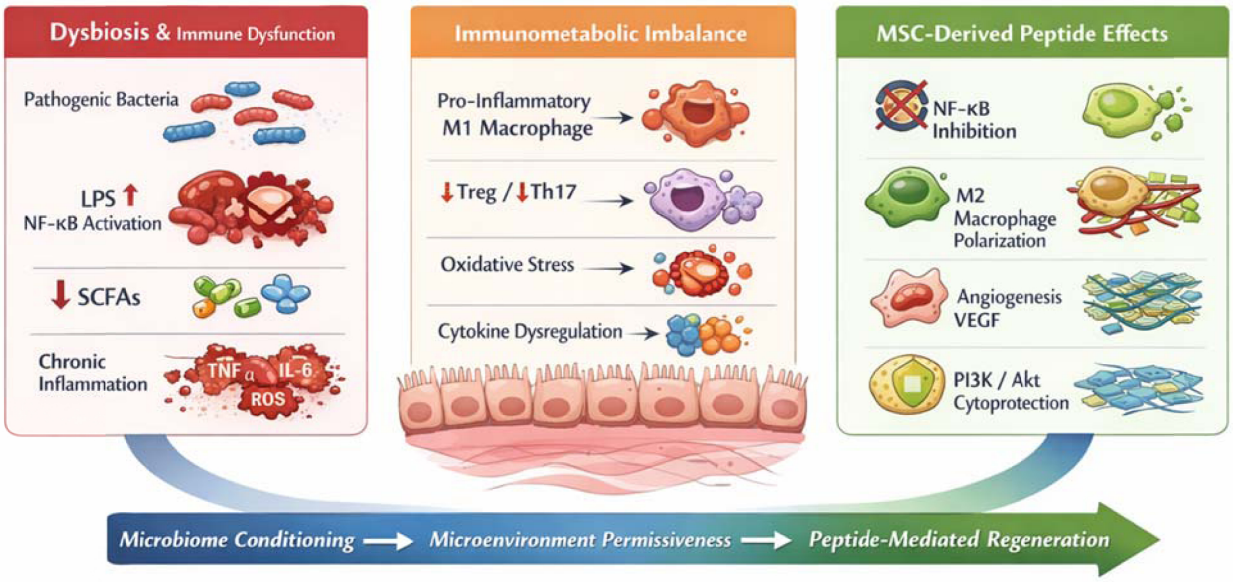

Fig. 1. Mechanistic representation of the microbiome-peptidome axis in tissue regulation.

and adaptive immune responses and reprogram the inflammatory set points associated with chronic disease progression; these include short chain fatty acids (SCFAs), bile acid derivatives, and tryptophan metabolites [22].

Because immune responses are intimately linked to cellular metabolism (described as "immunometabolism"), metabolite-driven changes in nutrient sensing and redox balance can reprogram immune-cell function and influence whether inflammation resolves with direct implications for tissue-repair capacity [23]. When dysbiosis interferes with these metabolite networks and barrier-determined immune regulation, the host shifts towards sustained low-grade inflammation as well as maladaptive immune-metabolic signaling, generating a less regenerative-permissive microenvironment [24]. Concurrently, the "peptidome" arm of this axis is modeled by stem-cell–derived bioactive molecules because therapeutic benefit is being attributed more and more to the MSC secretome (including peptide/protein regulators and other paracrine synergies) as opposed to durable engraftment of infused cells [25].

MSC-secretome–based therapies are therefore poised as cell-free regenerative therapies with the potential to modulate inflammation, promote angiogenic repair, and mediate extracellular matrix remodeling via orchestrated paracrine signaling [26]. Nonetheless, the effectiveness and functional phenotype of MSC paracrine factors depends on local cues from the microenvironment; inflammatory signals, hypoxia, and metabolic stress can reprogram stromal cell function as well as secretome composition and signaling cascades in recipient tissues [27]. This reliance is a mechanism for synergy; dependence on microbiome-mediated barrier status, systemic inflammation, and immunometabolic tone can pre-condition tissues towards immune resolution and metabolic stability, priming their responsiveness to regenerative peptide signals rather than having this modulate effect progressively blunted by immune resistance [28]. As such, microbiome-targeted interventions (including durable probiotics) should be considered upstream microenvironment-conditioning modalities, while stem-cell–mediated peptides serve as downstream repair effectors to generate a complimentary and multi-axis strategy for inflammatory and degenerative disease contexts [29]. The coordinated interaction between microbiome-derived immunometabolic regulation and MSC-derived peptide signaling defines a mechanistic framework in which microenvironment conditioning enhances regenerative responsiveness (c.f. Fig. 1).

3. Functional properties of *Lactobacillus reuteri* DSMZ 17648

L. reuteri DSMZ 17648 is an example of strain-specific probiotic that has been investigated for host

microbial ecology modulation, immune regulation and gastrointestinal homeostasis effects not implicit to generic species-level effects. Unlike other wide-spectrum probiotics DSMZ 17648 successfully coaggregates with pathogens like *Helicobacter pylori*, which can lead to a decreased colonization and inflammation of the stomach [30]. Strain-specific probiotic activities also encompass modulation of gut microbiota composition and metabolic products, leading to stimulation of favorable microbial metabolic functions (e.g., production of short-chain fatty acids) and out-competition against pathogenic taxa [31]. Apart from microbial competition, *L. reuteri* has been shown to influence host immune pathways through interaction with epithelial and immune cells, resulting in modulation of cytokine profiles and strengthened regulatory immune effects in preclinical as well as clinical conditions [32].

From a mechanistic point of view, *L. reuteri* could interact with host pattern recognition receptors and affect signaling cascades (e.g., TLR-mediated pathways) involved in the regulation of innate immune activation and subsequent adaptive responses, thereby promoting an anti-inflammatory environment [33]. The ability of *L. reuteri* to support the function of epithelial barriers, which include increasing tight junction integrity as well as mucosal resistance, has been shown in both animal models and human observational studies and was implicated in maintaining the mucosal defense against luminal antigens and microbial translocation [34]. Besides immunoregulation and barrier effects, strain-specific effects of *L. reuteri* on systemic metabolic endpoints are demonstrated by transformations in microbial metabolites and clinical symptoms related to dysbiosis that improve in some small exploratory clinical trials [35]. The strain-specific functional properties of *L. reuteri* DSMZ 17648, including its clinical efficacy in *H. pylori* adjunct therapy and its pathogen co-aggregation mechanisms, are summarized in Table 1.

4. Biological activity of stem cell derived peptides

Peptides derived from mesenchymal stem cells (MSC), which are bioactive constituents of the larger MSC secretome, have recently emerged as dominant mediators of the regenerative and immunomodulatory properties associated with stem cell therapy. MSCs do not act via stable engraftment or direct cellular replacement but rather achieve their therapeutic effects mainly by paracrine/paracrinemediated pathways, which deliver a variety of proteins, peptides, cytokines, and growth factors that together orchestrate tissue healing and immune regulation [38]. At the molecular level MSC-produced peptides attenuate overactivation of pro-inflammatory pathways, like NF-κB and STAT signaling, while promoting a regulatory phenotype by either expanding T regs or skewing macrophages toward reparative (M2-like) phenotypes. This transition from proinflammatory amplification to regulated resolution may be especially pertinent in chronic inflammatory disorders with ongoing cytokine dysregulated and immune exhaustion [39, 40].

Apart from immunomodulation, MSC peptides demonstrated pro-angiogenic features by acting on endothelial cell survival mechanisms, induction of vascular endothelial growth factor (VEGF)-associated signaling and microvascular remodeling. These effects are important in ischemic and degenerating microenvironments where perfusion is restricted and endogenous repair capability is impaired. By restoring the vascular support, peptide-driven signaling enhances oxygenation, metabolism stability and nutritional exchange in injured tissues [41–43]. Cytoprotection and regulation of apoptosis is yet another key MSC-produced peptide activity. These peptides can reduce apoptosis induced by oxidative stress and increase the resistance of cells to stress (inflammatory or hypoxic state) through controlling the PI3K/Akt and MAPK pathways. This role is crucial, particularly in tissues with compromised metabolism, where chronic inflammation alters mitochondrial homeostasis and energy status [44–47].

MSC-peptides also modulate the dynamics of ECM through control of fibroblasts activation and by regulating collagen deposition and enzymes that remodel matrix. Excessive ECM deposition is detrimental to the organization and functioning of scarred or inflamed tissue, and consequently manipulation of matrix turnover is a major therapeutic goal for regeneration [48, 49]. Crucially, the biological activity of peptides derived from stem-cell differ widely depending on the context. The inflammatory status, metabolic context, oxygen availability and immune milieu of the target tissue can profoundly influence not only the composition of the MSC secretome but also recipient cell responsiveness. Pro-inflammatory microenvironment can dampen the regenerating signaling or repurpose the peptide effect, while a balanced immune milieu promotes regeneration efficacy. This micro-environment dependence highlights the necessity for upstream conditioning interventions, including manipulation of the microbiome, to maximize therapeutic efficacy [50–52].

Peptide-based strategies have several advantages over cell-based approaches from a translational point of view, such as eliminating risk of unregulated

Table 1. Strain-specific functional properties of *L. reuteri* DSMZ 17648 and level of supporting evidence.

Category	Functional Domain	Key Findings	References
Clinical Evidence (*H. pylori* Adjunct Therapy)	Eradication efficacy & symptom improvement	Adjunct supplementation significantly increased *H. pylori* eradication rates and reduced gastrointestinal symptom severity compared to standard therapy alone; demonstrated favorable safety profile including non-viable (postbiotic) formulations.	[36]
Strain-Specific Mechanism	Co-aggregation with *H. pylori*	Non-viable DSMZ 17648 cells selectively co-aggregate with *H. pylori*, interfering with pathogen motility and mucosal adherence, thereby reducing bacterial load independent of colonization.	[30]
Microbial Ecology Modulation	Competitive exclusion & ecological interference	Demonstrates competitive binding behavior that may limit pathogen persistence and contribute to restoration of microbial balance in the gastric niche.	[37]
Immunological & Barrier Influence (Probiotic Class Effects)	Barrier integrity & immune signaling	Probiotic-mediated modulation of epithelial tight junctions, microbial metabolites, and mucosal immune pathways supports inflammatory resolution and epithelial resilience, although DSMZ 17648-specific immune studies remain limited.	[31]

proliferation, being easier to store and transport, and potentially having more predictable safety profiles. However, standardization, peptide characterization, batch-to-batch variation issue and regulatory position of peptides become critical when complex peptide mixtures are employed instead of well-defined molecular entities [53–55]. MSC-derived peptides constitute a biologically tenable and mechanistically flexible platform to repair tissues and recalibrate the immune system. However, their maximum effectiveness is likely to be achieved through coordinated programming with approaches that balance immune system and metabolic homeostasis - rendering this microbiome-peptidome axis a rational, multi-tier physiological circuit for therapeutic intervention.

5. Disease-oriented integration of the microbiome-peptidome axis

Relevance of the microbiome–peptidome axis is realized in disease-specific pathophysiologic conditions that feature chronic inflammation, barrier failure, metabolic dysregulation and defective regenerative signaling. Instead of being separate interventions, rather that act synergistically in multiple organ systems to which tissue repair is limited by immune dysregulation. The proposed intersections between microbial regulation, immune recalibration, and regenerative peptide activity across major inflammatory and degenerative conditions are summarized in Table 2. The disease-oriented convergence of microbiome dysregulation and regenerative peptide signaling across major inflammatory and degenerative conditions is illustrated in Fig. 2.

5.1. Gastrointestinal inflammatory disorders

In the presence of conditions such as inflammatory bowel disease (IBD) and chronic gastritis, dysbiosis-promoted immune activation and epithelial barrier loss conspire to establish a hostile mucosal microenvironment for endogenous repair [63]. A probiotic intervention targeting specific strains may help to lower pathogenic load; re-establish microbial homeostasis and periphery suppress non-specific pro-inflammatory mechanisms [64, 65]. At the same time, MSC-produced peptides might contribute to epithelium amelioration and lead to macrophage polarization regulation as well as angiogenesis repair. In this regard, stabilization of microbiomes may serve as an upstream-permissive influence on the augmentation of peptide-mediated mucosal regeneration [66, 67].

5.2. Metabolic and systemic inflammatory disorders

Metabolic and non-alcoholic fatty liver disease, obesity-related inflammation are associated with low-grade systemic inflammation partly driven by microbial-derived endotoxemia and immunometabolic dysfunction [68, 69]. Modulation of the resident microbiome is a proposed strategy to reduce circulating systemic inflammatory markers and as regulators of metabolic signaling cascades [70]. Other peptides derived from stem cells can also act by inhibiting inflammatory cascades and preventing apoptosis (and fibrosis) in metabolically

Table 2. Proposed microbiome–peptidome synergy across inflammatory and degenerative disease contexts.

Disease / Condition	Microbiome Effect	MSC-Derived Peptide Effect	Synergy Insight	References
Inflammatory Bowel Disease (IBD)	Gut microbial dysbiosis drives intestinal immune imbalance, barrier dysfunction, and local inflammation.	MSC secretome has immunomodulatory, anti-inflammatory, and regenerative effects on mucosa and immune cells.	A balanced microbiome may normalize immune signals and reduce chronic inflammation, enhancing secretome-mediated mucosal repair.	[56, 57]
Chronic Wound Healing	Commensal bacteria and probiotics contribute to immune regulation and epithelial repair, influencing inflammation resolution.	MSC secretome accelerates tissue repair, reduces immune dysregulation, and enhances cell infiltration and regeneration.	Microbial modulation of immune responses may prime local environments to become more receptive to secretome-driven regeneration.	[56, 58]
Autoimmune & Immune-Mediated Disorders	Gut dysbiosis is linked to systemic immune disturbances and chronic inflammatory signaling.	MSC secretome modulates immune cell activity, reducing pro-inflammatory cytokines and promoting regulatory phenotypes.	A healthier microbiome could reduce systemic inflammation, improving peptide-guided immune recalibration.	[57, 59]
Neuroinflammatory and Neurodegenerative Conditions	Gut–brain axis: microbial metabolites modulate neuroimmune signaling and CNS inflammation.	MSC secretome demonstrates anti-inflammatory, neuroprotective, and regenerative potential in preclinical models.	Balanced microbial-immune interactions may reduce neuroinflammatory burden, enhancing secretome impact on neuronal repair.	[60]
Neuroinflammatory and Neurodegenerative Conditions	Gut-brain axis: microbial metabolites modulate neuroimmune signaling and CNS inflammation.	MSC secretome demonstrates anti-inflammatory, neuroprotective, and regenerative potential in preclinical models.	Balanced microbial-immune interactions may reduce neuroinflammatory burden, enhancing secretome impact on neuronal repair.	[60, 61]
Respiratory & Multi-Organ Inflammation	Microbiome shapes immune axis beyond the gut, influencing respiratory and systemic inflammation.	MSC secretome has anti-inflammatory and immune-regulating effects across tissues.	Microbial regulation of systemic immunity may reduce baseline inflammation, facilitating secretome-mediated repair in multiple organs.	[25, 57, 59, 62]

stressed tissues. This dual target approach might act on upstream players (inflammatory triggers) and also on downstream damage in the tissue [71, 72].

5.3. Neuroinflammatory and neurodegenerative conditions

The evidence Increasing underlines the existence of such a gut–brain axis, where microbial metabolites affect central immune signaling and neuroinflammation. Systemic inflammation induced by dysbiosis may interfere with neural repair mechanisms [73, 74]. Microbiome-directed interventions might reduce peripheral inflammatory setpoints and impact neuroimmune signaling, which are expected to increase the responsiveness of neural tissue to regenerative peptides [75, 76]. MSC-related peptides may provide neuroprotection, anti-inflammation and angiogenesis support, indicating a multitarget regulation strategy in the pathological contexts of aging-associated neurodegeneration [77, 78].

5.4. Chronic wound healing and fibrotic disorders

Chronic wounds and fibrotic conditions involve persistent inflammation, impaired angiogenesis, and extracellular matrix imbalance [79, 80]. Probiotic-mediated modulation of systemic immune tone and barrier integrity may reduce inflammatory burden [81, 82]. MSC-derived peptides may accelerate re-epithelialization, stimulate angiogenesis, and regulate matrix remodeling. Here, microbiome conditioning may shift the wound microenvironment from inflammatory persistence toward regenerative competence [83].

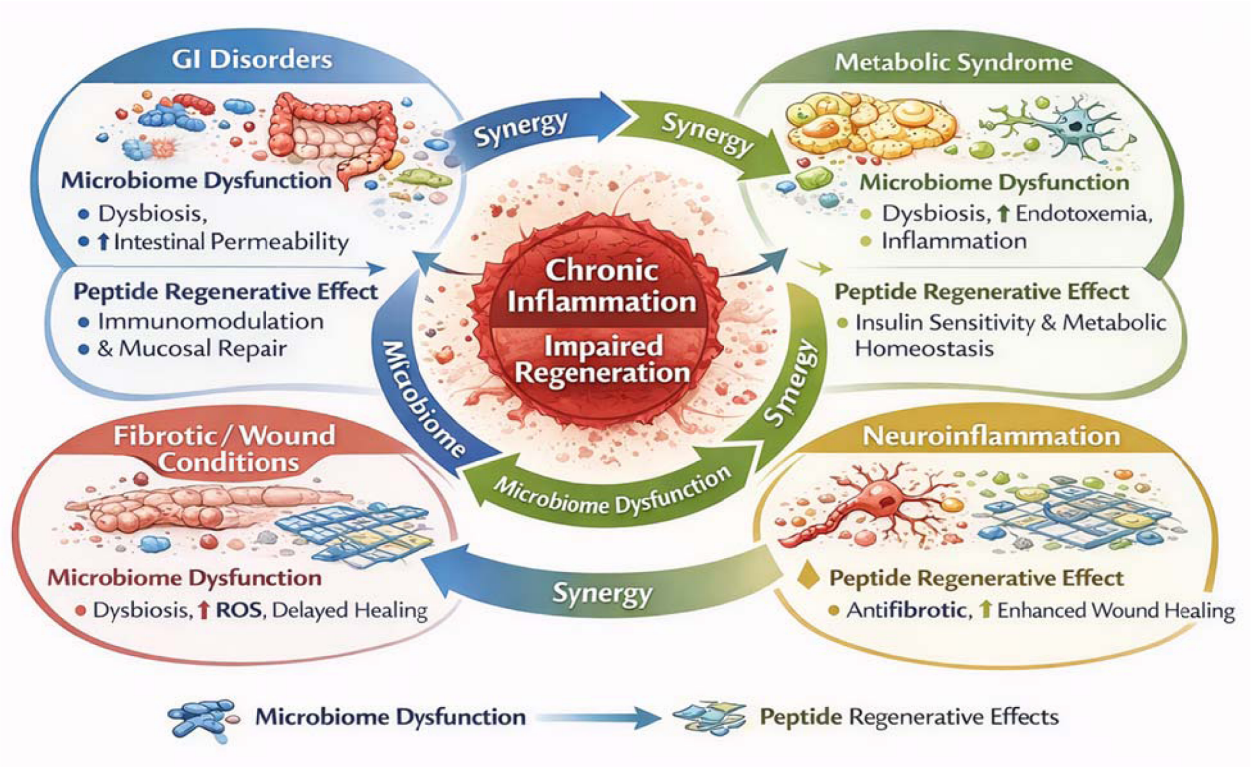

Fig. 2. Disease-oriented integration of the microbiome-peptidome axis.

5.5. Skeletal disorders and the gut–bone axis

The integration of microbiome-based interventions with stem cell-derived bioactive factors represents a potent frontier for therapeutic immunomodulation and systemic tissue regeneration. The probiotic *L. reuteri* has demonstrated significant clinical and preclinical efficacy in maintaining skeletal homeostasis, specifically by enhancing bone mineral density and preventing bone loss in both aging populations and estrogen-deficient models [84–86]. This therapeutic effect is driven by the species' capacity to restore immune equilibrium, particularly through the expansion and functional enhancement of Regulatory T cells (Tregs), which then stimulate the expression of osteogenic ligands such as Wnt10b to promote tissue repair [87, 88]. Complementing this microbial influence, stem cell-derived extracellular vesicles (EVs)—such as those from adipose tissue-derived stem cells function as rich peptidomic reservoirs, carrying essential signaling proteins like osteoprotegerin (OPG) that directly inhibit pathological bone resorption and support structural integrity [89, 90]. Synergistically, the interaction between these microbial metabolites and stem cell products including bone morphogenetic proteins (BMPs) and stem cell factors (SCF)—targets the gut-bone axis to provide a comprehensive biological network capable of managing complex inflammatory and degenerative diseases [91, 92]. By leveraging both the immunomodulatory power of the microbiome and the regenerative potential of stem cell-derived peptides, these synergistic therapeutics offer a multifaceted approach to restoring systemic homeostasis and promoting healing across various disease contexts [93, 94].

5.6. Autoimmune rheumatic diseases and the gut-immune axis

Disruption of gut microbial ecology and loss of immune tolerance are increasingly recognized as central contributors to the pathogenesis of autoimmune rheumatic diseases (ARDs) [95]. Mechanistically, dysbiosis may promote autoreactivity through molecular mimicry, whereby microbial mimotopes resemble host autoantigens and trigger aberrant adaptive immune responses [96]. In this context, L. reuteri has been investigated for its immunomodulatory potential, particularly its ability to promote regulatory T cell (Treg) expansion and enhance production of anti-inflammatory cytokines such as IL-10 [97, 98]. This regulatory shift counterbalances Th17-driven inflammatory pathways, which are critically

implicated in conditions such as rheumatoid arthritis and systemic lupus erythematosus [99]. Concurrently, stem cell–derived bioactive peptides and extracellular vesicles (EVs) contribute complementary regenerative and immunoregulatory effects [100, 101]. These paracrine mediators enhance epithelial barrier integrity and reduce permeability, thereby limiting systemic translocation of pro-inflammatory microbial ligands such as lipopolysaccharide (LPS), which can amplify autoimmune flares [102, 103]. At the intracellular level, both microbiome-mediated immune recalibration and stem cell–derived signaling may converge on key inflammatory pathways, including NF-κB and RANKL cascades, which are frequently overactivated in chronic autoimmune states [104, 105]. By integrating microbial suppression of pathobiont expansion with peptide-driven restoration of tolerogenic immune environments, the microbiome–peptidome axis represents a biologically coherent strategy for attenuating autoimmune inflammation and potentially slowing progressive tissue destruction [106, 107].

6. Translational challenges and therapeutic optimization strategies

While prior studies have explored microbiome modulation and MSC-secretome therapies independently, limited attention has been given to their coordinated integration within a unified therapeutic framework. Most existing literature focuses either on upstream immune regulation through microbiome interventions or on downstream regenerative mechanisms mediated by stem cell–derived factors. In contrast, the present framework emphasizes a sequential and mechanistically linked microbiome-peptidome axis, positioning immune conditioning as a strategy to enhance regenerative responsiveness.

Although there is strong mechanistic justification for microbiome-induced peptidome synergy, several application hurdles need to be addressed that sit between the bench and bedside for such holistic approach to become routine in clinics [108, 109]. Human microbiomes are themselves highly heterogeneous among individuals, and this diversity plays a role in probiotic responses including colonization efficiency, metabolite production, and subsequent modulation of the immune response [110, 111]. Precision microbiome profiling and multi-omics profiling have thus been suggested as a means to stratify patients and predict responsiveness to therapy in microbiome-targeted interventions [112, 113].

Formulation-wise, probiotic viability and stability have been the major issues, especially when formulated with bioactive peptides, which may have different storage conditions and delivery systems [114]. To improve probiotic survival through the gut, encapsulation methods such as microencapsulation and enteric-coated systems were studied to maintain the functional activity of probiotics [115]. In the same manner, stabilization of MSC-harvested peptide fractions necessitates sophisticated purification, lyophilization and sustained-release formulations to sustain bioactivity and reproducibility [116, 117].

One of the important aspects in microbiome-peptidome integration is therapeutic sequencing, where pre-treatment of immune-metabolic microenvironment and regenerative peptide signaling could make the target entity more prone to be responsive [118]. There is evidence from experimental studies indicating that both inflammatory tone and metabolic stress impact on MSC secretome composition and subsequent cellular effects, thus microbiome manipulation may act as a priming therapy before peptide infatuation [110, 120]. However, these sequencing patterns need to be further validated in well-designed clinical trials regarding the most appropriate time point of administration and dosage and duration of treatment.

Regulations constitute an additional formidable barrier, as probiotics are frequently classified as dietary supplements, while stem-cell–derived products could be subject to ATMP regulations or they could be considered as a biologics depending on their compositions and manufacturing quality [121]. The lack of standardized regulatory definitions for complex secretome-derived peptide cocktails is impeding approval pathways and standardization processes [122, 123]. The development of well-defined potency assays, molecular characterization pipelines and batch-to-batch consistency will be critical in the clinical translation process to ensure safety and reproducibility [124, 125].

Furthermore, the immunological complexity of chronic inflammatory diseases necessitates biomarker-guided therapeutic monitoring to evaluate microbiome shifts, inflammatory cytokine dynamics, and tissue-regeneration markers in parallel [126]. Integration of microbiome sequencing, metabolomics, and proteomic profiling may provide comprehensive insight into patient-specific responses and enable adaptive therapeutic adjustment [127, 128]. Such systems-biology–guided frameworks align with the emerging paradigm of precision regenerative medicine, where upstream immune stabilization and downstream regenerative activation are coordinated rather than independently targeted.

Finally, large-scale randomized controlled trials assessing combined microbiome–peptidome interventions remain scarce, and most current evidence is derived from independent probiotic or secretome

studies rather than integrated protocols [129]. Future translational research must therefore prioritize standardized combination-study designs, mechanistic biomarker endpoints, and long-term safety evaluation to validate the microbiome–peptidome axis as a clinically viable multi-tier therapeutic strategy.

Several limitations warrant consideration. As an integrative narrative synthesis, this framework is primarily based on mechanistic and preclinical evidence, with limited randomized combination trials currently available. Interindividual microbiome heterogeneity, strain-specific variability, and challenges in secretome standardization may influence therapeutic reproducibility. These factors should be carefully addressed in future translational investigations.

7. Conclusion

In summary, the evidence synthesized in this review supports a microbiome–peptidome axis as a mechanistically coherent, multi-tier framework for chronic inflammatory and degenerative diseases in which immune dysregulation, metabolic instability, barrier failure, and impaired repair are interdependent drivers. Within this paradigm, *L. reuteri* DSMZ 17648 is positioned as a strain-specific microbiome-conditioning modality that can stabilize microbial ecology and reduce inflammatory tone, whereas MSC-derived peptides represent downstream paracrine effectors capable of coordinating immunomodulation and tissue repair. Importantly, this integrated model has practical relevance: microbiome and inflammatory profiling may enable patient stratification and support a sequential strategy in which microbiome stabilization precedes peptide-based regenerative intervention in selected disease settings. To translate this concept, priority should be given to (i) biomarker-guided combination trials that test sequencing (microbiome priming vs co-administration vs peptides alone), (ii) standardized characterization and potency assays for secretome-derived peptide preparations with batch-to-batch controls, (iii) strain- and disease-specific validation of probiotic mechanisms and durability of microbiome shifts, and (iv) harmonized safety, regulatory, and long-term follow-up frameworks. Addressing these steps will determine whether microbiome conditioning can reliably enhance regenerative peptide efficacy and enable clinically actionable protocols.

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

Not applicable.

Data availability

No datasets were generated or analyzed during the current study.

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Author contributions

All authors contributed equally to the conception and design of the study.

References

1. Schreiner TG, Menéndez-González M, Schreiner OD, Ciobanu RC. Intrathecal therapies for neurodegenerative diseases: A review of current approaches and the urgent need for advanced delivery systems. *Biomedicines*. 2025;13(9):2167. https://doi.org/10.3390/biomedicines13092167.
2. Mallick R, Basak S, Chowdhury P, Bhowmik P, Das RK, Banerjee A, Paul S, Pathak S, Duttaroy AK. Targeting cytokine-mediated inflammation in brain disorders: Developing new treatment strategies. *Pharmaceuticals*. 2025;18(1):104. https://doi.org/10.3390/ph18010104.
3. Volonté C, Hu G, & Shaw CA, Viegas Jr C. Neuroprotection beyond neurons: Integrated biomarker-based and astroglia- or microglia-targeted approaches to combat neurodegenerative diseases. *Explor Neuroprotect Ther*. 2026;6:1004136. https://doi.org/10.37349/ent.2026.1004136.
4. Sun Y, Shao C, Duan H, Wang Z, Xu S, Wang C, Xiu J, Liu J, Wang X, Yao X, Gao Y. Dynamic evolution of the tumor immune microenvironment in malignant tumors and emerging therapeutic paradigms. *MedComm (Beijing)*. 2025;6(12). https://doi.org/10.1002/mco2.70496.
5. Sun N, Ogulur I, Mitamura Y, Yazici D, Pat Y, Bu X, Li M, Zhu X, Babayev H, Ardicli, S, Ardicli O. The epithelial barrier theory and its associated diseases. *Allergy*. 2024;79(12):3192–3237. https://doi.org/10.1111/all.16318.
6. Feng JJ, Maddirala NR, Saint Fleur A, Zhou F, Yu D, Wei F, Zhang Y. Gut microbiome and immune system crosstalk in chronic inflammatory diseases: A narrative review of mechanisms and therapeutic opportunities. *Microorganisms*. 2025;13(11):2516. https://doi.org/10.3390/microorganisms13112516.

7. Bermúdez-Humarán LG, Chassaing B, Langella P. Exploring the interaction and impact of probiotic and commensal bacteria on vitamins, minerals and short chain fatty acids metabolism. *Microb Cell Fact.* 2024;23(1):172. https://doi.org/10.1186/s12934-024-02449-3.
8. Sandhu AH, Radhakrishnan A. Gut biome-mediated barriers to nutrient absorption: Investigating the impact of dysbiosis. *Microbiol Res (Pavia)*. 2025;16(11):241. https://doi.org/10.3390/microbiolres16110241.
9. Zhang S, Elbs-Glatz Y, Tao S, Schmitt S, Li Z, Rottmar M, Maniura-Weber K, Ren Q. Probiotics promote cellular wound healing responses by modulating the PI3K and TGF-β/Smad signaling pathways. *Cell Commun Signal*. 2025;23(1):195. https://doi.org/10.1186/s12964-025-02179-y.
10. Agha HM, Abdalqader MA, Hoh J, Wassouf Y, Al-Saadawi KAAA, Mohammed AA, Alsayadi MMS. Sheep umbilical cord mesenchymal stem cells: Biological characteristics, ethical considerations, and translational applications. *AUIQ Complement Biol Syst*. 2026;3(1):1–17. https://doi.org/10.70176/3007-973X.1051.
11. Dionisio F, Domingues CPF, Rebelo JS, Monteiro F, Nogueira T. The impact of non-pathogenic bacteria on the spread of virulence and resistance genes. *Int J Mol Sci.* 2023;24(3):1967. https://doi.org/10.3390/ijms24031967.
12. Yoshihara M, Wagner M, Damdimopoulos A, Zhao C, Petropoulos S, Katayama S, Kere J, Lanner F, Damdimopoulou P. In reply: Revisiting claims of the continued absence of functional germline stem cells in adult ovaries. *Stem Cells.* 2023;41(2):205–206. https://doi.org/10.1093/stmcls/sxac084.
13. Rosson E, Lux F, David L, Godfrin Y, Tillement O, Thomas E. Focus on therapeutic peptides and their delivery. *Int J Pharm.* 2025;675:125555. https://doi.org/10.1016/j.ijpharm.2025.125555.
14. Magenheim J, Maestro MA, Sharon N, Herrera PL, Murtaugh LC, Kopp J, Sander M, Gu G, Melton DA, Ferrer J, Dor Y. Matters arising: Insufficient evidence that pancreatic β cells are derived from adult ductal Neurog3-expressing progenitors. *Cell Stem Cell*. 2023;30(4):488–497.e3. https://doi.org/10.1016/j.stem.2023.03.003.
15. Ismail NI, Nawawi KNM, Hsin DCC, Hao KW, Mahmood NRKN, Chearn GLC, Wong Z, Tamil AM, Joseph H, Raja Ali RA. Probiotic containing Lactobacillus reuteri DSM 17648 as an adjunct treatment for Helicobacter pylori infection: A randomized, double-blind, placebo-controlled trial. *Helicobacter*. 2023;28(6). https://doi.org/10.1111/hel.13017.
16. Buckley M, Lacey S, Doolan A, Goodbody E, Seamans K. The effect of Lactobacillus reuteri supplementation in Helicobacter pylori infection: A placebo-controlled, single-blind study. *BMC Nutr*. 2018;4(1):48. https://doi.org/10.1186/s40795-018-0257-4.
17. Han N, Jia L, Su Y, Du J, Guo L, Luo Z, Liu Y. Lactobacillus reuteri extracts promoted wound healing via PI3K/AKT/β-catenin/TGFβ1 pathway. *Stem Cell Res Ther*. 2019;10(1):243. https://doi.org/10.1186/s13287-019-1324-8.
18. Zhang P, Wu X, Liang S, Shao X, Wang Q, Chen R, Zhu W, Shao C, Jin F, Jia C. A dynamic mouse peptidome landscape reveals probiotic modulation of the gut-brain axis. *Sci Signal*. 2020;13(642). https://doi.org/10.1126/scisignal.abb0443.
19. KarakayalıEM, Tuğlu Mİ. The contribution of probiotics to combined cellular therapy in skin wound healing in diabetic rats. *Turk J Trauma Emerg Surg*. 2025;31(10):925–936. https://doi.org/10.14744/tjtes.2025.37711.
20. Mafe AN, Büsselberg D. The effect of microbiome-derived metabolites in inflammation-related cancer prevention and treatment. *Biomolecules*. 2025;15(5):688. https://doi.org/10.3390/biom15050688.
21. Zhao MA, Chu J, Feng S, Guo C, Xue B, He K, Li L. Immunological mechanisms of inflammatory diseases caused by gut microbiota dysbiosis: A review. *Biomed Pharmacother*. 2023;164:114985. https://doi.org/10.1016/j.biopha.2023.114985.
22. Yu S, Zhang M, Dou Z, Tian B, Lu J. Gut microbiota metabolites in the immunoregulation of enteritis: Research progress. *Front Immunol*. 2025;16. https://doi.org/10.3389/fimmu.2025.1706472.
23. Singer BD, Chandel NS. Immunometabolism of pro-repair cells. *J Clin Invest*. 2019;129(7):2597–2607. https://doi.org/10.1172/JCI124613.
24. Shen Y, Fan N, Ma S, Cheng X, Yang X, Wang G. Gut microbiota dysbiosis: Pathogenesis, diseases, prevention, and therapy. *MedComm (Beijing)*. 2025;6(5). https://doi.org/10.1002/mco2.70168.
25. Trigo CM, Rodrigues JS, Camões SP, Solá S, Miranda JP. Mesenchymal stem cell secretome for regenerative medicine: Where do we stand? *J Adv Res*. 2025;70:103–124. https://doi.org/10.1016/j.jare.2024.05.004.
26. Agha HM, Abdalqader MA, Hoh J, Wassouf Y, Al-Saadawi KAA, Mohammed AA, Alsayadi MMS. Mesenchymal stem cells as cornerstones of regenerative medicine: Mechanisms, applications, and future perspectives. *AUIQ Complement Biol Syst*. 2025;2(3):21–32. https://doi.org/10.70176/3007-973X.1042.
27. Jaraba-Álvarez WV, Uscanga-Palomeque AC, Sanchez-Giraldo V, Madrid C, Ortega-Arellano H, Halpert K, Quintero-Gil C. Hypoxia-induced metabolic reprogramming in mesenchymal stem cells: Unlocking the regenerative potential of secreted factors. *Front Cell Dev Biol*. 2025;13. https://doi.org/10.3389/fcell.2025.1609082.
28. Hu T, Liu CH, Lei M, Zeng Q, Li L, Tang H, Zhang N. Metabolic regulation of the immune system in health and diseases: Mechanisms and interventions. *Signal Transduct Target Ther*. 2024;9(1):268. https://doi.org/10.1038/s41392-024-01954-6.
29. Ebigbo N, Long A, Do P, Coughlin L, Poulides N, Jewell T, Gan S, Zhan X, Koh AY. Optimizing precision probiotics for mitigating graft-versus-host disease. *Microorganisms*. 2025;13(4):706. https://doi.org/10.3390/microorganisms13040706.
30. Smolinska S, Popescu FD, Zemelka-Wiacek M. A review of the influence of prebiotics, probiotics, synbiotics, and postbiotics on the human gut microbiome and intestinal integrity. *J Clin Med*. 2025;14(11):3673. https://doi.org/10.3390/jcm14113673.
31. Abdul Manan M. The role of probiotics in personalized therapeutics: Advances in gut microbe-driven interventions. *Microbe*. 2025;8:100497. https://doi.org/10.1016/j.microb.2025.100497.
32. Luo Z, Chen A, Xie A, Liu X, Jiang S, Yu R. Limosilactobacillus reuteri in immunomodulation: Molecular mechanisms and potential applications. *Front Immunol*. 2023;14. https://doi.org/10.3389/fimmu.2023.1228754.
33. Mu Q, Tavella VJ, Luo XM. Role of Lactobacillus reuteri in human health and diseases. *Front Microbiol*. 2018;9. https://doi.org/10.3389/fmicb.2018.00757.
34. Peng Y, Ma Y, Luo Z, Jiang Y, Xu Z, Yu R. Lactobacillus reuteri in digestive system diseases: Focus on clinical trials and mechanisms. *Front Cell Infect Microbiol*. 2023;13. https://doi.org/10.3389/fcimb.2023.1254198.
35. Ojetti V, Petruzziello C, Migneco A, Candelli M, Saviano A. Impact of oral administration of Lactobacillus reuteri LMG-P 27481 on human gut microbiota diversity and function: A pilot study. *Biomedicines*. 2025;13(11):2840. https://doi.org/10.3390/biomedicines13112840.

36. Ismail NI, Nawawi KNM, Hsin DCC, Hao KW, Mahmood NRKN, Chearn GLC, Wong Z, Tamil AM, Joseph H, Raja Ali RA. Probiotic containing Lactobacillus reuteri DSM 17648 as an adjunct treatment for Helicobacter pylori infection: A randomized, double-blind, placebo-controlled trial. *Helicobacter*. 2023;28(6). https://doi.org/10.1111/hel.13017.
37. Holz C, Busjahn A, Mehling H, Arya S, Boettner M, Habibi H, Lang C. Significant reduction in Helicobacter pylori load in humans with non-viable Lactobacillus reuteri DSM17648: A pilot study. *Probiotics Antimicrob Proteins*. 2015;7(2):91–100. https://doi.org/10.1007/s12602-014-9181-3.
38. Chu T, Xiao Z, Xun C, Yang C, Lu M, Wang Y, Chen H, Chen P. Peptidomic profiling of mesenchymal stem cell-derived extracellular vesicles and anti-inflammatory activity of degraded peptides. *Int Immunopharmacol*. 2025;152:114452. https://doi.org/10.1016/j.intimp.2025.114452.
39. Hoseinzadeh A, Esmaeili SA, Sahebi R, Melak AM, Mahmoudi M, Hasannia M, Baharlou R. Fate and long-lasting therapeutic effects of mesenchymal stromal/stem-like cells: Mechanistic insights. *Stem Cell Res Ther*. 2025;16(1):33. https://doi.org/10.1186/s13287-025-04158-z.
40. Chi Y, Jiang H, Yin Y, Zhou X, Shao Y, Li Y, Rao J. Macrophage signaling pathways in health and disease: From bench to bedside applications. *MedComm (Beijing)*. 2025;6(7). https://doi.org/10.1002/mco2.70256.
41. Łabędź-Masłowska A, Vergori L, Kędracka-Krok S, Karnas E, Bobis-Wozowicz, Sekuła-Stryjewska M, Sarna M, Andriantsitohaina R, Zuba-Surma EK. Mesenchymal stem cell-derived extracellular vesicles exert pro-angiogenic and pro-lymphangiogenic effects in ischemic tissues by transferring various microRNAs and proteins including ITGa5 and NRP1. *J Nanobiotechnology*. 2024;22(1):60. https://doi.org/10.1186/s12951-024-02304-y.
42. Lungu CN, Gurau G, Mehedinti MC. Pro-angiogenic bioactive molecules in vascular morphogenesis: Integrating endothelial cell dynamics. *Curr Issues Mol Biol*. 2025;47(10):851. https://doi.org/10.3390/cimb47100851.
43. Tao H, Han Z, Han ZC, Li Z. Proangiogenic features of mesenchymal stem cells and their therapeutic applications. *Stem Cells Int*. 2016;2016. https://doi.org/10.1155/2016/1314709.
44. Giacomini C, Granéli C, Hicks R, Dazzi F. The critical role of apoptosis in mesenchymal stromal cell therapeutics and implications in homeostasis and normal tissue repair. *Cell Mol Immunol*. 2023;20(6):570–582. https://doi.org/10.1038/s41423-023-01018-9.
45. Chen Z, Xia X, Yao M, Yang Y, Ao X, Zhang Z, Guo L, Xu X. The dual role of mesenchymal stem cells in apoptosis regulation. *Cell Death Dis*. 2024;15(4):250. https://doi.org/10.1038/s41419-024-06620-x.
46. Silva-Carvalho AÉ, Cardoso MH, Alencar-Silva T, Bogéa GMR, Carvalho JL, Franco OL, Saldanha-Araujo F. Dissecting the relationship between antimicrobial peptides and mesenchymal stem cells. *Pharmacol Ther*. 2022;233:108021. https://doi.org/10.1016/j.pharmthera.2021.108021.
47. Wang S, Zhang C, Niyazi S, Zheng L, Li J, Zhang W, Xu M, Rong R, Yang C, Zhu T. A novel cytoprotective peptide protects mesenchymal stem cells against mitochondrial dysfunction and apoptosis induced by starvation via Nrf2/Sirt3/FoxO3a pathway. *J Transl Med*. 2017;15(1):33. https://doi.org/10.1186/s12967-017-1144-5.
48. Boaru DL, De Leon-Oliva D, De Castro-Martinez P, Garcia-Montero C, Fraile-Martinez O, García-González B, Pérez-González I, Alhaddadin MNM, Barrena-Blázquez S, Lopez-Gonzalez L, de la Torre B. Extracellular matrix dysregulation in aging, calcification, and cancer diseases: Insights into cellular senescence, inflammation, and novel therapeutic strategies. *Int J Biol Sci*. 2025;21(15):6808–6881. https://doi.org/10.7150/ijbs.119301.
49. Guillamat-Prats R. The role of MSC in wound healing, scarring and regeneration. *Cells*. 2021;10(7):1729. https://doi.org/10.3390/cells10071729.
50. Arun M, Rajasingh S, Madasamy P, Rajasingh J. Immunomodulatory and regenerative functions of MSC-derived exosomes in bone repair. *Bioengineering*. 2025;12(8):844. https://doi.org/10.3390/bioengineering12080844.
51. Li Y, Jin M, Guo D, Shen S, Lu K, Pan R, Sun L, Zhang H, Shao J, Pan G. Unveiling the immunogenicity of allogeneic mesenchymal stromal cells: Challenges and strategies for enhanced therapeutic efficacy. *Biomed Pharmacother*. 2024;180:117537. https://doi.org/10.1016/j.biopha.2024.117537.
52. Bagno LL, Salerno AG, Balkan W, Hare JM. Mechanism of action of mesenchymal stem cells (MSCs): Impact of delivery method. *Expert Opin Biol Ther*. 2022;22(4):449–463. https://doi.org/10.1080/14712598.2022.2016695.
53. Afonso AL, Cavaleiro CT, Castanho MARB, Neves V, Cavaco M. The potential of peptide-based inhibitors in disrupting protein–protein interactions for targeted cancer therapy. *Int J Mol Sci*. 2025;26(7):3117. https://doi.org/10.3390/ijms26073117.
54. Długosz-Pokorska A, Gach-Janczak K. Peptide-based strategies for overcoming taxol-resistance in cancer therapy: A narrative review. *Pharmacol Rep*. 2025;77(6):1627–1638. https://doi.org/10.1007/s43440-025-00795-6.
55. Zane D, Feldman PL, Sawyer T, Sobol Z, Hawes J. Development and regulatory challenges for peptide therapeutics. *Int J Toxicol*. 2021;40(2):108–124. https://doi.org/10.1177/1091581820977846.
56. Rajesh A, Ju EDE, Oxford KA, Harman RM, Van de Walle GR. The mesenchymal stromal cell secretome promotes tissue regeneration and increases macrophage infiltration in acute and methicillin-resistant Staphylococcus aureus-infected skin wounds in vivo. *Cytotherapy*. 2024;26(11):1400–1410. https://doi.org/10.1016/j.jcyt.2024.06.007.
57. Preethy S, Ranganathan N, Raghavan K, Dedeepiya VD, Ikewaki N, Abraham SJK. Integrating the synergy of the gut microbiome into regenerative medicine: Relevance to neurological disorders. *J Alzheimers Dis*. 2022;87(4):1451–1460. https://doi.org/10.3233/JAD-220313.
58. Wang AYL, Aviña AE, Liu YY, Kao HK. Microbial allies in skin trauma recovery: From immune modulation to engineered probiotic therapeutics. *Burns Trauma*. 2026;14. https://doi.org/10.1093/burnst/tkaf068.
59. Azad T, Wu F, Mao J, Zhu J, Wang Y, Zhou X, Hong K, Xie H, Qiu X, Li B, Zhang L. Exploring the therapeutic potential of MSC-derived secretomes in neonatal care: Focus on BPD and NEC. *Stem Cell Res Ther*. 2025;16(1):476. https://doi.org/10.1186/s13287-025-04616-8.
60. Amodeo G, Galimberti G, Niada S, Giannasi C, Della Morte E, Franchi S, Riboldi B, Ceruti S, Brini AT, Sacerdote P. Cell-free therapies for chronic pain: The rise of the mesenchymal stem cell secretome. *Brain Sci*. 2025;15(12):1263. https://doi.org/10.3390/brainsci15121263.
61. Wang X, Liu M, Cao L, Huang H, Yang J, Zhang H, Xu Z. Gut microbiota–neuroinflammation axis: A new mechanism and therapeutic target for comorbid depression in epilepsy. *Brain Behav Immun Health*. 2025;50:101150. https://doi.org/10.1016/j.bbih.2025.101150.
62. Sari MI, Jusuf NK, Munir D, Putra A, Putra IB, Bisri T, Farhat F, Ilyas S, Muhar A. Mesenchymal stem cell secretome therapy on inflammation: A systematic review. *J Pharm Pharmacogn Res*. 2024;12(1):39–49. https://doi.org/10.56499/jppres23.1726_12.1.39.

63. Fava F, Danese S. Intestinal microbiota in inflammatory bowel disease: Friend or foe? *World J Gastroenterol*. 2011;17(5):557. https://doi.org/10.3748/wjg.v17.i5.557.
64. Tegegne BA, Kebede B. Probiotics, their prophylactic and therapeutic applications in human health development: A review of the literature. *Heliyon*. 2022;8(6):e09725. https://doi.org/10.1016/j.heliyon.2022.e09725.
65. Caliman-Sturdza OA, Vaz JA, Lupaescu AV, Lobiuc A, Bran C, Gheorghita RE. Antioxidant and anti-inflammatory activities of probiotic strains. *Int J Mol Sci*. 2026;27(2):1079. https://doi.org/10.3390/ijms27021079.
66. Zou Z, Liu Y, Zhang X, Cao J, Wei P, Huang Y, Jing W, Zhao B, Wang M. Angiogenesis-facilitating and inflammation-modulating SIS-based patches coupled with functional peptides for abdominal wall repair. *Mater Today Bio*. 2026;37:102795. https://doi.org/10.1016/j.mtbio.2026.102795.
67. Lu D, Xu Y, Liu Q, Zhang Q. Mesenchymal stem cell–macrophage crosstalk and maintenance of inflammatory microenvironment homeostasis. *Front Cell Dev Biol*. 2021;9. https://doi.org/10.3389/fcell.2021.681171.
68. Milano W, Carizzone F, Foia M, Marchese M, Milano M, Saetta B, Capasso A. Obesity and its multiple clinical implications between inflammatory states and gut microbiotic alterations. *Diseases*. 2022;11(1):7. https://doi.org/10.3390/diseases11010007.
69. Castro AM, Macedo-de la Concha LE, Pantoja-Meléndez CA. Low-grade inflammation and its relation to obesity and chronic degenerative diseases. *Rev Med Hosp Gen Mex*. 2017;80(2):101–105. https://doi.org/10.1016/j.hgmx.2016.06.011.
70. Peña-Durán E, García-Galindo JJ, López-Murillo LD, Huerta-Huerta A, Balleza-Alejandri LR, Beltrán-Ramírez A, Anaya-Ambriz EJ, Suárez-Rico DO. Microbiota and inflammatory markers: A review of their interplay, clinical implications, and metabolic disorders. *Int J Mol Sci*. 2025;26(4):1773. https://doi.org/10.3390/ijms26041773.
71. He J, Fu J, Wang R, Liu X, Yao J, Xing W, Wang X, He Y. Tissue repair mechanisms of dental pulp stem cells: A comprehensive review from cutaneous regeneration to mucosal healing. *Curr Issues Mol Biol*. 2025;47(7):509. https://doi.org/10.3390/cimb47070509.
72. Gao G, Zhang Z, Wang Q, Xie Z, Liu B, Huang H. A peptide alleviated oxidative damages in L02 cells and mice liver. *Biochem Biophys Res Commun*. 2024;734:150643. https://doi.org/10.1016/j.bbrc.2024.150643.
73. Banfi D, Moro E, Bosi A, Bistoletti M, Cerantola S, Crema F, Maggi F, Giron MC, Giaroni C, Baj A. Impact of microbial metabolites on microbiota–gut–brain axis in inflammatory bowel disease. *Int J Mol Sci*. 2021;22(4):1623. https://doi.org/10.3390/ijms22041623.
74. Kearns R. Gut–brain axis and neuroinflammation: The role of gut permeability and the kynurenine pathway in neurological disorders. *Cell Mol Neurobiol*. 2024;44(1):64. https://doi.org/10.1007/s10571-024-01496-z.
75. Liu C, Yang SY, Wang L, Zhou F. The gut microbiome: Implications for neurogenesis and neurological diseases. *Neural Regen Res*. 2022;17(1):53. https://doi.org/10.4103/1673-5374.315227.
76. Abdol Samat HN, Razali NN, Mahadzir H, Tengku Muhammad TS, Ling KH, Mansor NI, Abidin SZ. The interplay of inflammation and gut-microbiota dysbiosis in Alzheimer's disease: Mechanisms and therapeutic potential. *Int J Mol Sci*. 2025;26(18):8905. https://doi.org/10.3390/ijms26188905.
77. Cui CX, Shao XN, Li YY, Qiao L, Lin JT, Guan LH. Therapeutic potential of mesenchymal stem cells in neurodegenerative diseases. *World J Stem Cells*. 2025;17(8). https://doi.org/10.4252/wjsc.v17.i8.107717.
78. Trinh QD, Mai HN, Pham DT. Application of mesenchymal stem cells for neurodegenerative diseases therapy discovery. *Regen Ther*. 2024;26:981–989. https://doi.org/10.1016/j.reth.2024.09.014.
79. Schilrreff P, Alexiev U. Chronic inflammation in non-healing skin wounds and promising natural bioactive compounds treatment. *Int J Mol Sci*. 2022;23(9):4928. https://doi.org/10.3390/ijms23094928.
80. Martin P, Pardo-Pastor C, Jenkins RG, Rosenblatt J. Imperfect wound healing sets the stage for chronic diseases. *Science*. 2024;386(6726). https://doi.org/10.1126/science.adp2974.
81. Canchy L, Kerob D, Demessant A, Amici J. Wound healing and microbiome: An unexpected relationship. *J Eur Acad Dermatol Venereol*. 2023;37(S3):7–15. https://doi.org/10.1111/jdv.18854.
82. Shedaliya U, Adwani G, Anju TR, Krishnakumar A, Kumar A. Role of the microbiome in diabetic wound healing: Implications for new therapeutic approaches. *Arch Microbiol*. 2025;207(9):208. https://doi.org/10.1007/s00203-025-04399-9.
83. Chen D, Hao H, Fu X, Han W. Insight into reepithelialization: How do mesenchymal stem cells perform? *Stem Cells Int*. 2016;2016. https://doi.org/10.1155/2016/6120173.
84. Shaw CA, Verstrate M, Graniczkowska K, Risoen KR, Dini P, Weimer BC. The use of stem cells and organoids for modeling host-microbe interactions in low-biomass tissues. *Front Cell Infect Microbiol*. 2025;15:1641366. https://doi.org/10.3389/fcimb.2025.1641366.
85. Samiei M, Fathi M, Barar J, Fathi N, Amiryaghoubi N, Omidi Y. Bioactive hydrogel-based scaffolds for the regeneration of dental pulp tissue. *J Drug Deliv Sci Technol*. 2021;64:102600. https://doi.org/10.1016/j.jddst.2021.102600.
86. Garaci E, Russo MA, Pariano M, Puccetti M, Fabi C, Balucchi S, Bellet MM, Ricci M, Fini M, Romani L. Innovative approaches to medical rehabilitation: regeneration, immune training, homeostasis, and microbiome synergy. *Int J Mol Sci*. 2025;26(17):8687. https://doi.org/10.3390/ijms26178687.
87. Zaiss MM, Jones RM, Schett G, Pacifici R. The gut-bone axis: how bacterial metabolites bridge the distance. *J Clin Invest*. 2019;129(8):3018–3028. https://doi.org/10.1172/JCI128521.
88. Yan J, Herzog JW, Tsang K, Brennan CA, Bower MA, Garrett WS, Sartor BR, Aliprantis AO, Charles JF. Gut microbiota induce IGF-1 and promote bone formation and growth. *Proc Natl Acad Sci USA*. 2016;113(47):E7554–E7563. https://doi.org/10.1073/pnas.1607235113.
89. Smith BJ, Hatter B, Washburn K, Graef-Downard J, Ojo BA, El-Rassi GD, Cichewicz RH, Payton M, Lucas EA. Dried plum's polyphenolic compounds and carbohydrates contribute to its osteoprotective effects and exhibit prebiotic activity in estrogen deficient C57BL/6 mice. *Nutrients*. 2022;14(9):1685. https://doi.org/10.3390/nu14091685.
90. Wesemann DR. Microbes and B cell development. *Adv Immunol*. 2015;125:155–178. https://doi.org/10.1016/bs.ai.2014.09.005.
91. Liu X, Zhang H, Shi G, Zheng X, Chang J, Lin Q, Tian Z, Yang H. The impact of gut microbial signals on hematopoietic stem cells and the bone marrow microenvironment. *Front Immunol*. 2024;15:1338178. https://doi.org/10.3389/fimmu.2024.1338178.

92. Li K, Jiang Y, Wang N, Lai L, Xu S, Xia T, Yue X, Xin H. Traditional Chinese medicine in osteoporosis intervention and the related regulatory mechanism of gut microbiome. *Am J Chin Med.* 2023;51(8):1957–1981. https://doi.org/10.1142/S0192415X23500866.
93. Qu S, Yu S, Ma X, Wang R. Medicine food homology" plants promote periodontal health: antimicrobial, anti-inflammatory, and inhibition of bone resorption. *Front Nutr*. 2023;10:1193289. https://doi.org/10.3389/fnut.2023.1193289.
94. Li B, Liu M, Wang Y, Gong S, Yao W, Li W, Gao H, Wei M. Puerarin improves the bone microenvironment to inhibit OVX-induced osteoporosis via modulating SCFAs released by the gut microbiota and repairing intestinal mucosal integrity. *Biomed Pharmacother*. 2020;132:110923. https://doi.org/10.1016/j.biopha.2020.110923.
95. Manfredo Vieira S, Hiltensperger M, Kumar V, Zegarra-Ruiz D, Dehner C, Khan N, Costa FRC, Tiniakou E, Greiling T, Ruff W, Barbieri A. Translocation of a gut pathobiont drives autoimmunity in mice and humans. *Science.* 2018;359(6380):1156–1161. https://doi.org/10.1126/science.aar7201.
96. Ruff WE, Dehner C, Kim WJ, Pagovich O, Aguiar CL, Yu AT, Roth AS, Vieira SM, Kriegel C, Adeniyi O, Mulla MJ. Pathogenic autoreactive T and B cells cross-react with mimotopes expressed by a common human gut commensal to trigger autoimmunity. *Cell Host Microbe.* 2019;26(1):100–113. https://doi.org/10.1016/j.chom.2019.05.003.
97. Luo Z, Chen A, Xie A, Liu X, Jiang S, Yu R. *Limosilactobacillus reuteri* in immunomodulation: molecular mechanisms and potential applications. *Front Immunol.* 2023;14:1228754. https://doi.org/10.3389/fimmu.2023.1228754.
98. Smolinska S, Popescu FD, Zemelka-Wiacek M. A Review of the Influence of Prebiotics, Probiotics, Synbiotics, and Postbiotics on the Human Gut Microbiome and Intestinal Integrity. *J Clin Med.* 2025;14(11):3673. https://doi.org/10.3390/jcm14113673.
99. Katsuyama T, Tsokos GC, Moulton VR. Aberrant T cell signaling and subsets in systemic lupus erythematosus. *Front Immunol.* 2018;9:1088. https://doi.org/10.3389/fimmu.2018.01088.
100. Hoseinzadeh A, Esmaeili SA, Sahebi R, Melak AM, Mahmoudi M, Hasannia M, Baharlou R. Fate and long-lasting therapeutic effects of mesenchymal stromal/stem-like cells: mechanistic insights. *Stem Cell Res Ther*. 2025;16(1):33. https://doi.org/10.1186/s13287-025-04158-z.
101. Chu T, Xiao Z, Xun C, Yang C, Lu M, Wang Y, Chen H, Chen P. Peptidomic profiling of mesenchymal stem cell-derived extracellular vesicles and anti-inflammatory activity of degraded peptides. *Int Immunopharmacol.* 2025;152:114452. https://doi.org/10.1016/j.intimp.2025.114452.
102. Ocansey DKW, Wang L, Wang J, Yan Y, Qian H, Zhang X, Xu W, Mao F. Mesenchymal stem cell–gut microbiota interaction in the repair of inflammatory bowel disease: an enhanced therapeutic effect. *Clin Transl Med.* 2019;8(1):31. https://doi.org/10.1186/s40169-019-0251-8.
103. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes.* 2007;56(7):1761–1772. https://doi.org/10.2337/db06-1491.
104. Chi Y, Jiang H, Yin Y, Zhou X, Shao Y, Li Y, Rao J. Macrophage signaling pathways in health and disease: from bench to bedside applications. *MedComm.* 2025;6(7):e70256. https://doi.org/10.1002/mco2.70256.
105. Tanaka S, Tanaka Y. RANKL as a therapeutic target of rheumatoid arthritis. *J Bone Miner Metab.* 2021;39(1):106–112. https://doi.org/10.1007/s00774-020-01159-1.
106. Azad T, Wu F, Mao J, Zhu J, Wang Y, Zhou X, Hong K, Xie H, Qiu X, Li B, Zhang L. Exploring the therapeutic potential of MSC-derived secretomes in neonatal care: focus on BPD and NEC. *Stem Cell Res Ther*. 2025;16(1):476. https://doi.org/10.1186/s13287-025-04616-8.
107. Williams KL, Enslow R, Suresh S, Beaton C, Hodge M, Brooks AE. Using the microbiome as a regenerative medicine strategy for autoimmune diseases. *Biomedicines.* 2023;11(6):1582. https://doi.org/10.3390/biomedicines11061582.
108. Bautista J, Echeverría CE, Maldonado-Noboa I, Ojeda-Mosquera S, Hidalgo-Tinoco C, López-Cortés A. The human microbiome in clinical translation: From bench to bedside. *Front Microbiol*. 2025;16. https://doi.org/10.3389/fmicb.2025.1632435.
109. Yaqub MO, Jain A, Joseph CE, Edison LK. Microbiome-driven therapeutics: From gut health to precision medicine. *Gastrointest Disord*. 2025;7(1):7. https://doi.org/10.3390/gidisord7010007.
110. Azad MAK, Sarker M, Li T, Yin J. Probiotic species in the modulation of gut microbiota: An overview. *Biomed Res Int.* 2018;2018:9478630. https://doi.org/10.1155/2018/9478630.
111. Vonaesch P, Garneau JR, Dominguez-Bello MG. From global to local: Rethinking the design of probiotic intervention strategies. *Trends Microbiol*. 2025. https://doi.org/10.1016/j.tim.2025.11.009.
112. Shahid U. Microbiome-guided precision medicine: Mechanistic insights, multi-omics integration, and translational horizons. *J Precis Med Health Dis*. 2025;3:100018. https://doi.org/10.1016/j.premed.2025.100018.
113. Kashyap PC, Chia N, Nelson H, Segal E, Elinav E. Microbiome at the frontier of personalized medicine. *Mayo Clin Proc*. 2017;92(12):1855–1864. https://doi.org/10.1016/j.mayocp.2017.10.004.
114. Sun C, Zhang Z, Sun Y, Sun X, Jin Y, Zhu J, Yu J, Wu T. Enteric delivery of probiotics: Challenges, techniques, and activity assays. *Foods*. 2025;14(13):2318. https://doi.org/10.3390/foods14132318.
115. Sun C, Wang S, Yang L, Song H. Advances in probiotic encapsulation methods to improve bioactivity. *Food Biosci*. 2023;52:102476. https://doi.org/10.1016/j.fbio.2023.102476.
116. Mocchi M, Bari E, Marrubini G, Bonda AF, Perteghella S, Tartara F, Cofano F, Perna GD, Giovannelli L, Mandracchia D, Sorlini M. Freeze-dried mesenchymal stem cell-secretome pharmaceuticalization: Optimization of formulation and manufacturing process robustness. *Pharmaceutics*. 2021;13(8):1129. https://doi.org/10.3390/pharmaceutics13081129.
117. Driscoll J, Yan IK, Patel T. Development of a lyophilized off-the-shelf mesenchymal stem cell-derived acellular therapeutic. *Pharmaceutics*. 2022;14(4):849. https://doi.org/10.3390/pharmaceutics14040849.
118. Williams KL, Enslow R, Suresh S, Beaton C, Hodge M, Brooks AE. Using the microbiome as a regenerative medicine strategy for autoimmune diseases. *Biomedicines*. 2023;11(6):1582. https://doi.org/10.3390/biomedicines11061582.
119. Ragni E, Perucca Orfei C, De Luca P, Mondadori C, Viganò M, Colombini A, de Girolamo L. Inflammatory priming enhances mesenchymal stromal cell secretome potential as a

clinical product for regenerative medicine approaches through secreted factors and EV-miRNAs: The example of joint disease. *Stem Cell Res Ther*. 2020;11(1):165. https://doi.org/10.1186/s13287-020-01677-9.

120. Ocansey DKW, Wang L, Wang J, Yan Y, Qian H, Zhang X, Xu W, Mao F. Mesenchymal stem cell–gut microbiota interaction in the repair of inflammatory bowel disease: An enhanced therapeutic effect. *Clin Transl Med*. 2019;8(1). https://doi.org/10.1186/s40169-019-0251-8.
121. Spacova I, Binda S, Ter Haar JA, Henoud S, Legrain-Raspaud S, Dekker J, Espadaler-Mazo J, Langella P, Martín R, Pane M, Ouwehand AC. Comparing technology and regulatory landscape of probiotics as food, dietary supplements and live biotherapeutics. *Front Microbiol*. 2023;14. https://doi.org/10.3389/fmicb.2023.1272754.
122. Kim JH, Yang H, Kim MW, Cho KS, Kim DS, Yim HE, Atala Z, Ko IK, Yoo JJ. Delivery of the recombinant protein cocktail identified by stem cell-derived secretome analysis accelerates kidney repair after renal ischemia-reperfusion injury. *Front Bioeng Biotechnol*. 2022;10. https://doi.org/10.3389/fbioe.2022.848679.
123. Giannasi C, Niada S, Della Morte E, Casati S, Orioli M, Gualerzi A, Brini AT. Towards secretome standardization: Identifying key ingredients of MSC-derived therapeutic cocktail. *Stem Cells Int*. 2021;2021:3086122. https://doi.org/10.1155/2021/3086122.
124. Capelli C, Cuofano C, Pavoni C, Frigerio S, Lisini D, Nava S, Quaroni M, Colombo V, Galli F, Bezukladova S, Panina-Bordignon P. Potency assays and biomarkers for cell-based advanced therapy medicinal products. *Front Immunol*. 2023;14. https://doi.org/10.3389/fimmu.2023.1186224.
125. Torggler R, Margreiter E, Marksteiner R, Thurner M. Potency assay development: A keystone for clinical use. *In: Advanced therapy medicinal products*. 2023:13–28. https://doi.org/10.1007/978-3-031-30040-0_2.
126. Katsanos AH, Kyriakidi K, Karassa FB, Politis D, Skamnelos A, Christodoulou DK, Katsanos KH. Biomarker development in chronic inflammatory diseases. In: Biomarkers for endometriosis. *Cham: Springer*. 2017:41–75. https://doi.org/10.1007/978-3-319-59856-7_3.
127. Tegegne HA, Savidge TC. Gut microbiome metagenomics in clinical practice: Bridging the gap between research and precision medicine. *Gut Microbes*. 2025;17(1). https://doi.org/10.1080/19490976.2025.2569739.
128. Yang SY, Han SM, Lee JY, Kim KS, Lee JE, Lee DW. Advancing gut microbiome research: The shift from metagenomics to multi-omics and future perspectives. *J Microbiol Biotechnol*. 2025;35:e2412001. https://doi.org/10.4014/jmb.2412.12001.
129. Markowiak P, Śliżewska K. Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients*. 2017;9(9):1021. https://doi.org/10.3390/nu9091021.