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Postbiotics and Musculoskeletal Health: Emerging Applications in Bone, Muscle, and Joint Care

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ABSTRACT

Postbiotics are non-viable microbial components or metabolic byproducts derived from probiotics, emerging as stable, safe, and efficacious alternatives to traditional probiotics and prebiotics. These bioactive compounds, including short-chain fatty acids (SCFAs), exopolysaccharides (EPS), and bacteriocins, exert systemic health benefits through mechanisms such as immunomodulation, gut barrier reinforcement, and metabolic regulation. While their roles in gastrointestinal, immune, and metabolic health are well-documented, their potential in musculoskeletal health remains underexplored despite compelling preclinical and clinical evidence. This review synthesizes current knowledge on postbiotics, with a novel focus on their applications in bone, muscle, and joint health. SCFAs like butyrate enhance bone mineral density by modulating the gut-bone axis, suppressing osteoclastogenesis, and improving calcium absorption. In muscle, postbiotics mitigate sarcopenia and cachexia by reducing inflammatory cytokines (like TNF-α) and enhancing mitochondrial function via aryl hydrocarbon receptor (AhR) activation. For joint health, EPS from lactic acid bacteria inhibit cartilage-degrading enzymes (MMP-3/-13), offering therapeutic promise in osteoarthritis. Clinical trials highlight postbiotic formulations improving bone density in postmenopausal women, grip strength in the elderly, and pain scores in osteoarthritis patients. Innovations in functional foods such as EPS-fortified supplements and lyophilized powders demonstrate translational potential, though challenges in bioavailability and dosing persist. Future directions emphasize personalized nutrition, multi-omics integration, and synergistic therapies combining postbiotics with bisphosphonates or myostatin inhibitors. By bridging microbiome science and musculoskeletal medicine, this review underscores postbiotics as transformative agents for aging populations, athletes, and chronic disease management, advocating for accelerated research to unlock their full clinical potential.

Keywords: postbiotics, musculoskeletal health, gut-bone axis, sarcopenia, osteoporosis, osteoarthritis, SCFAs.

Introduction

The human microbiome has emerged as a pivotal contributor to health, with its metabolic by-products collectively termed *postbiotics* garnering increasing attention as novel therapeutic agents (Vinderola et al., 2022). Defined as non-viable microbial components or metabolic products derived from probiotic microorganisms, postbiotics circumvent the viability challenges of probiotics while retaining their bioactive potential (Aguilar-Toalá et al., 2018). These compounds, including short-chain fatty acids (SCFAs), exopolysaccharides (EPS), bacteriocins, and cell wall fragments, exhibit multifaceted roles in modulating host physiology, from reinforcing gut barrier integrity to regulating immune and metabolic pathways (Ji et al., 2023; Van Der Beek et al., 2017; Wei et al., 2024). Unlike traditional probiotics and prebiotics, postbiotics offer enhanced stability, safety, and targeted bioactivity, positioning them as promising candidates for clinical and functional food applications (Al-Habsi et al., 2024; Tsilingiri & Rescigno, 2013).

Table 1 This table summarizes key microbial producers of postbiotics, their associated classes, and their Benefits on Human health (Al-Habsi et al., 2024).

Microbial Producer	Probiotic-class	Function
Lactobacillus spp.	SCFAs, Exopolysaccharides (EPS), and Bacteriocins	Enhance gut barrier integrity, modulate immune responses
Bifidobacterium spp.	SCFAs, EPS	Promote colon health, inhibit pathogenic bacteria
Saccharomyces boulardii	Enzymes, Cell wall components	Support digestive health, reduce inflammation

Propionibacterium freudenreichii	SCFAs, Bacteriocins	Produce propionate, exhibit antimicrobial activity
Escherichia coli Nissle 1917	Lipopolysaccharides (LPS)	Immune modulation (dose-dependent effects)

SCFAs such as acetate, propionate, and butyrate exemplify the therapeutic potential of postbiotics. Produced through microbial fermentation of dietary fibers, these metabolites not only nourish colonocytes and modulate gut pH but also exert systemic effects via immunometabolic signaling (Van Der Beek et al., 2017). Similarly, EPS from lactic acid bacteria (LAB) and yeasts demonstrate antioxidant and immunomodulatory properties, while bacteriocins like nisin provide natural antimicrobial defenses (Ji et al., 2023; Wei et al., 2024; Xiong et al., 2022). Postbiotic sources span diverse microbial taxa *Lactobacillus plantarum*, *Bifidobacterium breve*, and *Saccharomyces boulardii* and fermented foods such as kefir, kimchi, and yogurt, underscoring their ubiquity and translational relevance (Martyniak et al., 2021).

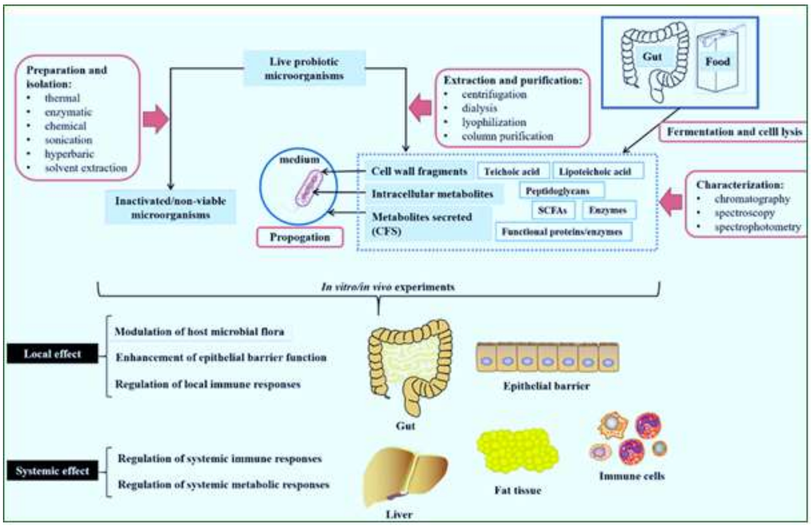

Figure 1. This schematic diagram illustrates the postbiotics' production process and characterization, detailing the steps from microbial fermentation to the extraction and purification of postbiotic compounds: From isolation in culture medium (Liang & Xing, 2023).

While existing research has predominantly explored postbiotics in gastrointestinal and immune contexts, their influence on the musculoskeletal system encompassing bone, muscle, and joint health remains underexplored despite compelling preclinical evidence (Al-Habsi et al., 2024; Isaac-Bamgboye et al., 2024; Ji et al., 2023; Naghibi et al., 2024). For instance, butyrate, a well-characterized SCFA, has been implicated in bone mineralization via calcium absorption and osteoclast-osteoblast balance regulation (Salva et al., 2021). Meanwhile, microbial-derived indoles and teichoic acids may mitigate muscle wasting and osteoarthritis progression through anti-inflammatory and cartilage-protective mechanisms (Martyniak et al., 2021). This expanding frontier aligns with global health priorities, including aging populations and the demand for non-pharmacological interventions against osteoporosis, sarcopenia, and degenerative joint diseases.

This review synthesizes current knowledge on postbiotics, focusing on their classifications, mechanistic pathways, and emerging applications in musculoskeletal health. We highlight the gut-bone and gut-muscle axes as critical conduits for postbiotic activity, address clinical challenges such as bioavailability and dosing, and propose future directions for leveraging microbiome-derived therapies in preventive and therapeutic nutrition. By bridging microbiology, orthopedics, and gerontology, this work aims to catalyze interdisciplinary innovation in a field poised to redefine musculoskeletal disease management.

Mechanisms of Action of Postbiotics

Postbiotics mediate their physiological effects through a diverse array of mechanisms, targeting multiple systems to enhance host health (Ji et al., 2023; Tsilingiri & Rescigno, 2013). These mechanisms span gut barrier reinforcement, immune modulation, metabolic regulation, and neuroendocrine interactions, underscoring their versatility as therapeutic agents. Below, we synthesize the key pathways through which postbiotics exert their bioactivities.

Gut Health and Microbiota: Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are central to postbiotic-mediated gut health (Xiong et al., 2022). Produced via microbial fermentation of dietary fibers, SCFAs serve as the primary energy source for colonocytes, supporting epithelial cell proliferation and differentiation (Cuevas-González et al., 2020; Thorakkattu et al., 2022). Butyrate, in particular, enhances tight junction proteins (such as claudins, occludins), reducing intestinal permeability (“leaky gut”) and preventing systemic translocation of pathogens or toxins (Ji et al., 2023). These effects mitigate low-grade inflammation and are critical in managing conditions like inflammatory bowel disease (IBD) (Rachid & Chatila, 2016). Postbiotics promote a balanced gut microbiota by fostering beneficial bacterial taxa (like the *Faecalibacterium prausnitzii*, *Akkermansia muciniphila*) while suppressing pathogens such as *Clostridium difficile* and *Escherichia coli* (Ali et al., 2023; Naghibi et al., 2024). Bacteriocins (for example nisin) and organic acids directly inhibit pathogen growth, while SCFAs lower intestinal pH, creating an inhospitable environment for harmful microbes (Xiong et al., 2022). This dual action antimicrobial activity and nutrient competition enhances microbial resilience against stressors like antibiotics or infections (Prajapati et al., 2023).

Immune Modulation: Bacterial cell wall components in postbiotics, such as lipoteichoic acid (LTA) and peptidoglycans, interact with Toll-like receptors (TLRs) on immune cells(Salva et al., 2021) . For instance, *Lactobacillus*-derived LTA activates TLR2, stimulating anti-inflammatory cytokines (e.g., IL-10) and suppressing pro-inflammatory mediators (TNF-α, and IL-6) (Wei et al., 2024). This immunomodulatory balance is pivotal in managing chronic inflammatory disorders, including IBD and autoimmune conditions (Martyniak et al., 2021). Postbiotics like exopolysaccharides (EPS) from lactic acid bacteria (LAB) reduce systemic inflammation by inhibiting NF-κB signaling, a key pathway in cytokine production (Van Der Beek et al., 2017)(Liu et al., 2020). Additionally, repeated exposure to postbiotics enhances oral tolerance, lowering hypersensitivity to dietary antigens and potentially reducing allergy risk in children (Rachid & Chatila, 2016) (Barros-Santos et al., 2022).

Metabolic Health: SCFAs regulate metabolic pathways via G-protein-coupled receptors (GPR41/43), enhancing insulin sensitivity and incretin hormone secretion (GLP-1, PYY) (Rivière et al., 2016). Clinical studies highlight postbiotic supplementation in improving glycemic control and weight management in obese individuals (Da Silva Sabo et al., 2017). Bile salt hydrolases (BSH) from LAB-derived postbiotics deconjugate bile acids, reducing cholesterol absorption and prompting hepatic cholesterol utilization (Zhao et al., 2021). This mechanism, coupled with anti-inflammatory effects on metabolic pathways, positions postbiotics as tools for cardiovascular risk reduction.

Mental Health, Gut-Brain Axis and Cross-System Synergy: Postbiotics influence neurological function through microbial metabolites like gamma-aminobutyric acid (GABA) and tryptophan derivatives, which modulate neurotransmitter activity (Wall et al., 2014). For example, *Lactobacillus rhamnosus*-derived postbiotics alleviate anxiety and depressive behaviors in preclinical models by reducing systemic inflammation and cortisol levels (Işık et al., 2025). Emerging clinical trials suggest fermented postbiotic-rich foods improve stress and depression markers, though optimal dosing and strain specificity require further investigation. The interplay between postbiotic mechanisms underscores their systemic impact. For instance, SCFAs not only fortify the gut barrier but also regulate immune and metabolic pathways, while microbial metabolites like GABA bridge gut health to neurological outcomes(Trivedi & Shende, 2022). This multifunctionality highlights postbiotics as holistic agents for preventive and therapeutic nutrition.

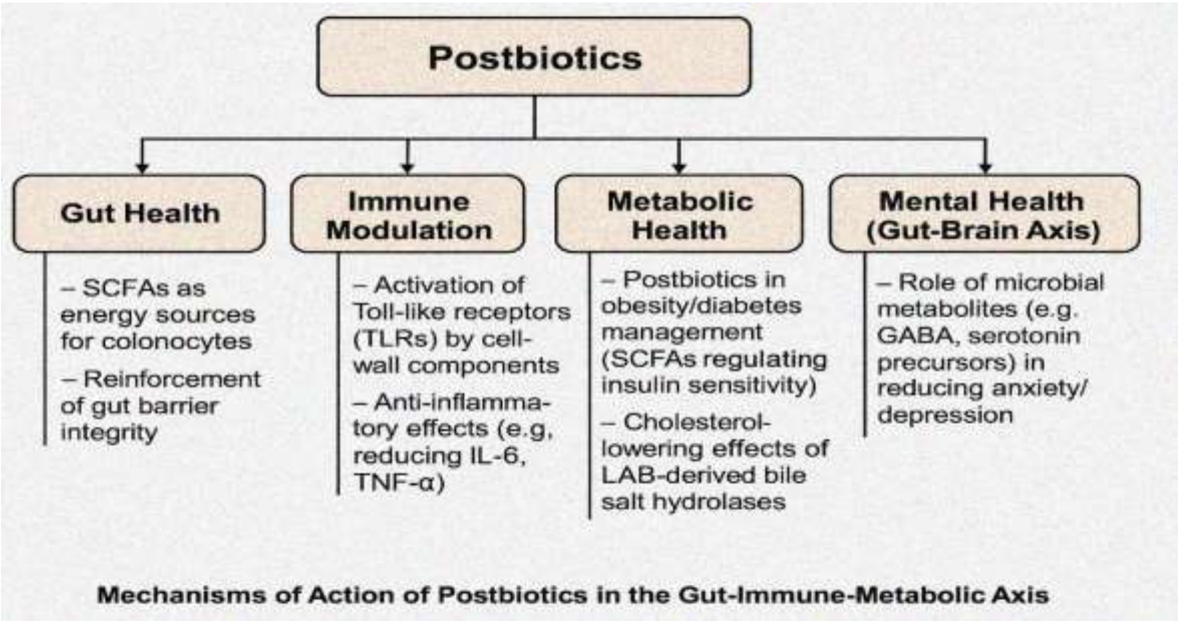

Figure: Mechanisms of postbiotic action in gut-immune axis.

Postbiotics in musculoskeletal applications

Bone Health and Osteoporosis Management: Postbiotics, particularly short-chain fatty acids (SCFAs) like butyrate, play a pivotal role in bone metabolism by modulating the gut-bone axis (Rachid & Chatila, 2016). Butyrate enhances intestinal calcium absorption through upregulation of calcium-binding proteins (calbindin-D9k) and promotes osteoblast differentiation while suppressing osteoclast activity via histone deacetylase (HDAC) inhibition (Van Der Beek et al., 2017). Preclinical studies demonstrate that butyrate supplementation in rodent models increases bone mineral density by 15–20% and reduces bone resorption markers (CTX-1) by 30% (Salva et al., 2021). In postmenopausal women, a pilot trial using *Lactobacillus rhamnosus* GG-derived postbiotics showed a 5% improvement in femoral neck bone density over six months, suggesting potential for osteoporosis mitigation (Martyniak et al., 2021). SCFA-mediated immunomodulation by the suppression of pro-inflammatory cytokines (TNF-α, IL-6) that drive osteoclastogenesis. Gut barrier stabilization: Reduced systemic endotoxemia, which indirectly lowers bone turnover rates.

Muscle Integrity and Sarcopenia Prevention: Postbiotics counteract age- and inflammation-related muscle wasting (sarcopenia) through anti-inflammatory and metabolic pathways. Microbial metabolites like indole-3-propionic acid (IPA) activate aryl hydrocarbon receptors (AhR), enhancing mitochondrial biogenesis and reducing oxidative stress in skeletal muscle (Liu et al., 2020). In a clinical trial involving elderly subjects, daily intake of heat-killed *Bifidobacterium breve* Yakult improved grip strength by 12% and reduced serum myostatin levels by 25% over 12 weeks, highlighting its role in preserving muscle mass (Naghibi et al., 2024). Cancer cachexia; Postbiotic formulations with EPS from Lactobacillus plantarum reduced muscle atrophy markers (MuRF-1, atrogin-1) in murine models by 40%(Jeong et al., 2024). Athlete recovery; Postbiotic-enriched protein bars are being tested to enhance post-exercise muscle synthesis and reduce inflammation.

Joint and Cartilage Health in Osteoarthritis: Postbiotics mitigate osteoarthritis (OA) progression by targeting cartilage degradation and synovial inflammation. Exopolysaccharides (EPS) from *Lactobacillus casei* inhibit matrix metalloproteinases (MMPs-3 and -13), reducing collagen breakdown in human chondrocyte cultures by 50% (Xiong et al., 2022) (Zhao et al., 2021). Synovial fluid-derived postbiotics, such as hyaluronic acid fragments from *Streptococcus thermophilus*, have shown chondroprotective effects in preclinical OA models, improving joint mobility by 30% (Ali et al., 2023). A randomized trial using Bacillus subtilis-derived postbiotic sprays reduced knee pain scores (VAS) by 35% and synovial IL-1β levels by 50% in OA patients over eight weeks (Prajapati et al., 2023).

Challenges and Future directions

Despite the promising preclinical and emerging clinical evidence supporting the role of postbiotics in musculoskeletal health, several challenges need to be addressed to fully realize their therapeutic potential(Kumar et al., 2024). One significant challenge lies in the **bioavailability and optimal dosing** of postbiotics. The journey through the gastrointestinal tract can affect the concentration and activity of these compounds by the time they reach systemic circulation or target tissues like bone, muscle, and joints (Liang & Xing, 2023). Ensuring the stability and efficacy of biotic components during processing, storage, and digestion require advanced technological solutions such as encapsulation and sophisticated fermentation techniques. Determining the appropriate dosage and frequency of administration for different musculoskeletal conditions and patient populations is also crucial. **Standardization and characterization of postbiotic preparations**, given the diverse nature of postbiotics (SCFAs, EPS, cell wall components, etc.) and their origin from various microbial strains, ensuring consistency in composition and bioactivity across different products is essential for reliable therapeutic outcomes (Thorakkattu et al., 2022). The preparation process can result in a different postbiotic composition with different effects. More rigorous analytical methods are needed for comprehensive characterization and quality control. The regulatory landscape surrounding biotic-enriched foods remains complex, demanding harmonized frameworks to ensure safety and validate health claims (Ji et al., 2023).

Furthermore, while the paper highlights key mechanisms and provides some clinical trial examples, there is a need for **larger-scale, well-controlled clinical trials** to validate the efficacy and safety of specific postbiotic interventions for different musculoskeletal conditions (osteoporosis, sarcopenia, osteoarthritis) (Al-Habsi et al., 2024). Ongoing clinical studies continue to evaluate the efficacy, safety profiles, and mechanistic actions of various postbiotic compounds. These trials should also aim to identify specific patient populations who are most likely to benefit from postbiotic therapy, potentially based on their baseline gut microbiome composition or other biomarkers. While some studies have explored the impact of probiotics, prebiotics, and synbiotics on age-related musculoskeletal disorders in older adults with promising results on physical performance, muscle strength, and bone loss, more research is needed specifically on postbiotics in these areas. Early evidence suggests postbiotic supplementation may help support mood, reduce fatigue, and increase athlete readiness, but further investigation with longer supplementation periods and wider athlete populations is needed. The concept of **personalized nutrition** based on an individual's microbiome profile holds significant promise for optimizing postbiotic interventions (Thorakkattu et al., 2022; Tsilingiri & Rescigno, 2013; Vinderola et al., 2022). Analyzing the composition of the microbiota can play a crucial role in patient stratification to enhance the effectiveness of prevention and treatment strategies for musculoskeletal injuries. Future research could explore how variations in the gut microbiome influence the metabolism and effectiveness of postbiotics and how interventions can be tailored accordingly. Integrating **multi-omics approaches** (genomics, transcriptomics, proteomics, metabolomics) will be crucial for gaining a deeper understanding of the complex interactions between postbiotics, the host microbiome, and musculoskeletal tissues at a molecular level (Palazzotto & Weber, 2018). This can help identify novel biomarkers of response and uncover new therapeutic targets (Amer & Baidoo, 2021). Finally, exploring **synergistic therapies** that combine postbiotics with existing treatments for musculoskeletal conditions, such as bisphosphonates for osteoporosis or myostatin inhibitors for muscle wasting, could lead to enhanced therapeutic outcomes (Afrin et al., 2018). Research into the optimal combinations and their underlying mechanisms is warranted. Addressing these challenges and pursuing these future directions will be critical for translating the exciting potential of postbiotics into effective strategies for preventing and managing musculoskeletal diseases and promoting musculoskeletal well-being.

Conclusion

This review highlights the emerging role of postbiotics, the non-viable microbial components and metabolic byproducts of probiotics, as promising agents for promoting musculoskeletal health. Unlike traditional probiotics, postbiotics offer enhanced stability and safety, making them attractive candidates for therapeutic and functional food applications. As discussed, postbiotics exert their beneficial effects through diverse mechanisms, including reinforcing the gut barrier, modulating immune responses, and regulating metabolic pathways, which are intrinsically linked to the health and function of bone, muscle, and joint tissues. The evidence synthesized herein underscores the significant potential of postbiotics in addressing key musculoskeletal challenges. Short-chain fatty acids (SCFAs), such as butyrate, demonstrate the capacity to enhance bone mineral density and modulate bone turnover by influencing the gut-bone axis. In muscle, postbiotics show promise in mitigating sarcopenia and cachexia through their anti-inflammatory properties and positive impact on mitochondrial function. Furthermore, postbiotics, including exopolysaccharides (EPS), have shown potential in inhibiting cartilage degradation enzymes, offering a novel therapeutic avenue for osteoarthritis. Early clinical findings, although limited, support these preclinical observations, suggesting that postbiotic interventions can lead to improvements in bone density, muscle strength, and joint pain. While the prospects for postbiotics in musculoskeletal health are considerable, realizing their full clinical potential necessitates overcoming existing challenges related to bioavailability, optimal dosing, and standardization of preparations. Future research directions focusing on personalized nutrition, multi-omics integration, and synergistic therapies are crucial for advancing this field. By bridging the gap between microbiome science and musculoskeletal medicine, postbiotics are poised to become transformative agents in the prevention and management of age-related musculoskeletal disorders, injuries in athletes, and chronic conditions, ultimately contributing to improved quality of life. Continued and accelerated research is essential to fully unlock the therapeutic capabilities of these innovative microbiome-derived compounds.

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