International Journal of Women's Health

Dovepress
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REVIEW

Gut Microbiota Has the Potential to Improve Sarcopenic Obesity in Menopausal Women by Regulating Estrogen

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Background: Sarcopenic obesity (SO) in menopausal women, characterized by concurrent skeletal muscle loss and visceral adiposity, is primarily driven by estrogen deficiency. Emerging evidence suggests that the gut microbiota, through its "estrobolome" function, may significantly influence SO pathogenesis by modulating estrogen metabolism and muscle-adipose crosstalk.

Objective: To systematically review the mechanisms linking the gut microbiota, estrogen metabolism, and SO risk in menopausal women.

Methods: We synthesized findings from animal models, mechanistic studies, and small-scale human trials investigating the microbiota-estrogen-muscle/adipose axis.

Results: Menopause reduced the abundance of the gut microbial β-glucuronidase, impairing enterohepatic estrogen recirculation. Dysbiosis activates the LPS-TLR4 pathway, promoting muscle catabolism via MuRF1 up-regulation and adipose inflammation. Short-chain fatty acids enhance insulin sensitivity through GLP-1 stimulation. Population studies have demonstrated reduced microbiota diversity and altered Firmicutes/Bacteroidetes ratios in postmenopausal women, which correlates with systemic inflammation and metabolic dysfunction. Intervention studies using combined soy isoflavones and probiotics have shown lipid benefits, but muscle effects remain unevaluated.

Conclusion: The gut microbiota-estrogen axis is a promising therapeutic target for menopausal SO; however, current evidence is limited to preclinical models and small human trials. Rigorous large-scale randomized controlled trials are essential to establish efficacy and safety before microbiota-based interventions can be recommended as adjunctive therapies.

Keywords: gut microbiota, sarcopenic obesity, menopause, estrobolome, therapeutic implications

Introduction

Sarcopenic obesity (SO), an emerging metabolic syndrome in postmenopausal women, is characterized by progressive loss of skeletal muscle mass and function coupled with abnormal visceral fat accumulation. Its health risks may substantially exceed those of sarcopenia or obesity alone.[1,2] Against the backdrop of accelerated global population aging, the prevalence of SO in women over 50 years of age is on the rise, with some cross-sectional studies reporting rates of 15–25%.[3] While the precipitous decline in estrogen levels is widely considered the core driver of this pathological process, emerging research suggests that the gut microbiota may play an underestimated role in regulating estrogen metabolism and muscle fat homeostasis through its unique "estrobolome" function.[4] It must be emphasized that the current evidence is largely derived from animal experiments and small-scale observational studies, with causal relationships yet to be firmly established. The precise role of gut microbiota in the development and progression of SO requires validation through large-scale prospective studies. This comprehensive review systematically examines the existing evidence regarding the putative influence of gut microbiota on SO risk in menopausal women via the modulation of estrogen metabolism, critically evaluates the underlying molecular mechanisms and methodological limitations, and explores potential translational applications. See Figure 1.

https://doi.org/10.2147/IJWH.S589117
Received: 15 December 2025
Accepted: 17 February 2026
Published: 26 February 2026

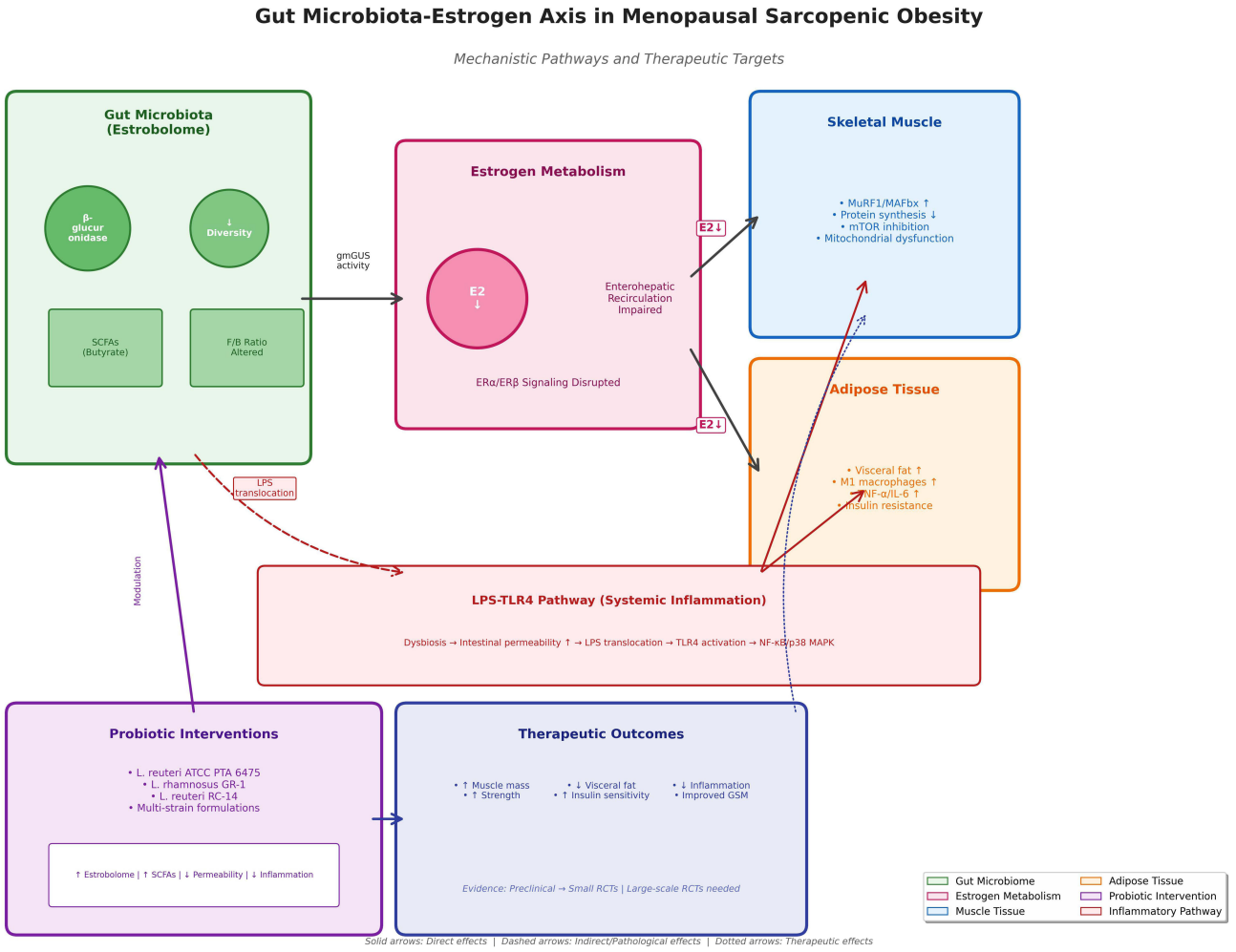

Figure 1 Overview of the gut microbiota-estrogen axis in menopausal sarcopenic obesity. The schematic shows bidirectional crosstalk between gut microbiota, estrogen metabolism, and peripheral tissues. Key mechanisms include: (1) reduced β-glucuronidase (gmGUS) activity impairing estrogen recirculation; (2) LPS-TLR4 pathway activation promoting muscle catabolism and adipose inflammation; (3) SCFA-mediated metabolic regulation. Probiotic interventions may benefit multiple menopause-related conditions including GSM, bone health, and metabolic dysfunction.

Pathophysiological Foundation and Clinical Burden of Menopausal Sarcopenic Obesity

Menopause is a critical window of physiological transition marked by profound hormonal alterations. The gradual cessation of ovarian function precipitates a dramatic reduction in circulating 17β-estradiol concentrations, typically declining from to 100–250 pg/mL during the reproductive years to below 10–20 pg/mL within a relatively compressed 12–24 month timeframe.[5] This hormonal shift correlates with clinically significant changes in body composition, including an approximately 0.6% annual reduction in skeletal muscle mass and a concomitant 22.3 cm^2 average increase in visceral adipose tissue area.[6] The pathogenic impact of estrogen deficiency appears multifaceted: at the muscular level, it likely attenuates anabolic signaling through the insulin-like growth factor 1 (IGF-1)/PI3K/AKT cascade while upregulating key catabolic mediators including muscle ring finger protein 1 (MuRF1) and muscle atrophy F-box protein (MAFbx), thereby disrupting protein homeostasis.[7] In adipose tissue, estrogen withdrawal appears to diminish suppressive effects on visceral fat deposition while promoting chronic low-grade inflammation.[8] Despite these well-documented mechanisms, the clinical application of hormone replacement therapy (HRT) demonstrates heterogeneous outcomes, with meta-analytical evidence suggesting only modest preservation of lean mass (approximately 0.06 kg reduction in loss) and potential cardiovascular complications.[2] This therapeutic inconsistency strongly implies the involvement of additional regulatory pathways in addition to simple estrogen replacement.[9] Intestinal microbiota, increasingly conceptualized as a "virtual endocrine organ", possesses a metabolic repertoire that vastly exceeds the host's genomic capabilities.[10] The

term "estrobolome", introduced in 2011, specifically denotes the collection of microbial genes responsible for estrogen metabolism, with β-glucuronidase (gmGUS) representing a key enzymatic component.[11] gmGUS-mediated deconjugation of hepatic estrogen-glucuronides within the intestinal lumen enables enterohepatic recirculation of bioactive estrogen, theoretically sustaining systemic estrogen pools.[12] Beyond estrogen modulation, gut microbes generate short-chain fatty acids (SCFAs), modify bile acid profiles, and modulate inflammatory cascades, all of which can directly affect muscle and adipose tissue metabolism independent of estrogen status.[13] Consequently, a biologically plausible hypothesis emerges wherein menopause-associated dysbiosis may exacerbate SO through dual mechanisms: impaired estrogen metabolism and direct pro-inflammatory effects. Conversely, targeted microbiome manipulation might partially ameliorate estrogen deficiency-induced metabolic dysfunction.[14] Nevertheless, this hypothesis remains largely speculative and supported principally by associative rather than definitive interventional data.[15]

The Estrobolome: Functional Architecture and Bidirectional Host-Microbe Crosstalk

The intricate interplay between gut microbiota and estrogen appears to manifest as a bidirectional relationship. Microbial gmGUS activity critically influences estrogen bioavailability. Comparative metagenomic studies have indicated that postmenopausal women exhibit reduced microbial β-glucuronidase (gmGUS) abundance and diversity compared to premenopausal individuals, potentially impairing enterohepatic estrogen recirculation.[16] Metagenomic analyses revealed that postmenopausal women exhibited a significantly reduced abundance of β-glucuronidase gene orthologs compared to premenopausal individuals, with gmGUS-producing taxa such as Clostridium spp. showing relative depletion, corresponding to a potential decline in enzymatic activity,[17] while potentially pathogenic Enterobacteriaceae may expand.[18] Preliminary causative evidence from murine models demonstrates that fecal microbiota transplantation (FMT) from high gmGUS-activity donors to ovariectomized (OVX) recipients can elevate serum estradiol levels by approximately 30% and increase muscle mass by 15%.[19] Conversely, estrogen itself appears to sculpt microbiota composition, as OVX models exhibit increased intestinal permeability and systemic translocation of bacterial products such as lipopolysaccharide (LPS).[20] Clinical investigations corroborate these findings: longitudinal studies report reduced microbiota diversity in postmenopausal women,[21] while metagenomic analyses reveal altered Firmicutes/Bacteroidetes ratios.[9] This bidirectional crosstalk potentially establishes a self-amplifying cycle in which estrogen deficiency promotes dysbiosis, which subsequently diminishes estrogen availability and collectively advances the SO pathophysiology.[22] However, the limited sample sizes and inherent species differences in these studies necessitate cautious extrapolation to the human populations.[23] In addition to estrogen-dependent pathways, the gut microbiota may modulate muscle metabolism through several direct mechanisms. SCFAs, particularly butyrate, potentially function as histone deacetylase (HDAC) inhibitors, activating mTOR signaling to promote protein synthesis while suppressing FOXO transcription factors to reduce proteolysis.[24] Experimental evidence from OVX mice indicates that butyrate supplementation may increase the muscle mass by 18%.[25] Propionates may enhance insulin sensitivity via GLP-1 stimulation.[26] In contrast, LPS-induced TLR4 activation may directly suppress muscle synthesis and upregulate MuRF1 expression.[27] Microbial metabolites such as indole-3-propionic acid can activate the aryl hydrocarbon receptor (AhR) to promote muscle stem cell proliferation.[28] Furthermore, emerging evidence suggests the remote modulation of muscle function through the vagus nerve-brain-muscle axis, although the specific mechanisms remain to be fully elucidated.[29] Although preclinical data support microbiota manipulation for muscle benefits,[30] definitive human muscle biopsy studies confirming these pathways in menopausal women are required.[31]

Microbiota-Adipose Tissue Interactions and Metabolic Consequences

In adipose tissue, gut microbiota may affect lipid deposition through bile acid metabolism and inflammatory modulation.[32] Estrogen suppresses preadipocyte differentiation and lipogenic enzyme expression via ERα,[33] dysbiosis may compromise its protective function.[34] Secondary bile acids, such as lithocholic acid, can theoretically improve metabolism through TGR5 activation, although excessive levels may impair intestinal barrier integrity.[35] OVX murine models have demonstrated that FMT can alter the bile acid pool composition, coincident with reduced visceral adiposity.[36] From an inflammatory perspective, dysbiosis-associated LPS elevation triggers M1 polarization of adipose tissue macrophages, promoting the secretion of TNF-α and IL-6.[37] These cytokines impair insulin sensitivity[38] and promote lipolysis, releasing free fatty acids that exacerbate muscle lipotoxicity.[39] Thus, the effects of microbiota on adipose tissue are likely to operate indirectly through the inflammatory

microenvironment and hormonal signal modulation.[40] Nevertheless, these observations are predominantly derived from animal models, human adipose tissue biopsy studies are scarce, and causal relationships require further validation.[41]

The therapeutic potential of microbiota modulation in menopause extends far beyond the management of sarcopenic obesity. Emerging evidence suggests that probiotic interventions may confer beneficial effects across multiple estrogen deficiency-related pathologies, providing a mechanistic rationale for their broader application in postmenopausal women's health. As highlighted by Stabile et al[42] the genitourinary syndrome of menopause (GSM)—affecting 25–50% of menopausal women—represents a critical domain where probiotic therapy demonstrates particular promise. The vaginal microbiota undergoes significant compositional shifts during menopause, characterized by depletion of Lactobacillus species and loss of the protective acidic environment, contributing to vaginal dryness, dyspareunia, and recurrent urinary tract infections.[42] Importantly, clinical trials have demonstrated that oral probiotic supplementation with specific Lactobacillus strains significantly improves vaginal health indices and restores microbiota composition in postmenopausal women,[43] suggesting that the "gut-vagina axis" may serve as a therapeutic target for GSM management.

The mechanistic parallels between probiotic effects on GSM and their potential utility in sarcopenic obesity are noteworthy. Both conditions share a common etiological foundation in estrogen deficiency-induced dysbiosis, characterized by compromised intestinal barrier function, systemic inflammation, and impaired metabolic homeostasis.[42,44] Probiotics may ameliorate these shared pathophysiological features through multiple convergent pathways: (1) restoration of intestinal barrier integrity, thereby reducing LPS translocation and systemic inflammatory burden;[45] (2) modulation of the estrobolome function, potentially enhancing circulating estrogen availability through β-glucuronidase-mediated deconjugation;[16,17] and (3) production of short-chain fatty acids (SCFAs) that exert anti-inflammatory and metabolic regulatory effects at distal sites including adipose tissue, muscle, and bone.[24–26]

Beyond GSM, probiotic interventions have demonstrated efficacy in other estrogen deficiency-related comorbidities. Recent meta-analytic evidence indicates that probiotic supplementation positively impacts postmenopausal bone health,[46] with specific strains such as Lactobacillus reuteri ATCC PTA 6475 showing capacity to reduce bone mineral density loss in osteopenic women.[47] The underlying mechanisms involve probiotic-mediated suppression of osteoclastogenic cytokines (TNF-α, RANKL) and enhancement of intestinal calcium absorption.[46,47] Similarly, cardiovascular risk factors—exacerbated by menopausal estrogen decline—may be modulated by probiotics through bile salt hydrolase-mediated reduction of cholesterol levels and SCFA-induced improvements in insulin sensitivity.[44] These pleiotropic effects underscore the systemic nature of microbiota-host interactions and suggest that targeted probiotic interventions may address the multifaceted metabolic consequences of menopause through interconnected molecular pathways.[42,44]

The clinical implications of these findings for sarcopenic obesity management are substantial. Given that probiotic therapy demonstrates measurable benefits in GSM—a condition sharing common mechanistic roots with sarcopenic obesity in estrogen deficiency and dysbiosis—there exists a compelling rationale for extrapolating these therapeutic strategies to the management of body composition disorders in menopausal women. The observation that combined soy isoflavones and probiotics improve lipid profiles while potentially influencing estrogen metabolism[40,48] suggests that multi-modal microbiota-targeted interventions may address the complex inter-organ crosstalk between gut, muscle, and adipose tissue. However, as Stabile et al appropriately caution, current evidence regarding probiotic efficacy in menopausal populations is limited by small sample sizes, heterogeneity in strain selection and dosing regimens, and variability in outcome measures.[42] Large-scale randomized controlled trials specifically evaluating probiotic effects on muscle mass, strength, and physical function in women with sarcopenic obesity remain essential to establish evidence-based therapeutic recommendations. See Figure 2.

Current clinical evidence remains limited and heterogeneous. An open-label FMT trial involving 20 postmenopausal women with metabolic syndrome demonstrated that after transplanting microbiota from young healthy donors for three months, recipients' alpha diversity increased, E2 rose from 18 pg/mL to 26 pg/mL, visceral fat decreased by 8.5 cm^2, and grip strength improved by 1.8 kg.[49] However, partial parameters rebounded after six months, indicating that sustained intervention may be necessary for durable effects.[50] Probiotic investigations have shown that Lactobacillus reuteri DSM 17938 may increase E2 levels and improve body composition in OVX mice, although human results remain inconsistent.[51] Combined soy isoflavones and probiotics have demonstrated synergistic effects in select RCTs, potentially increasing E2 by 28% and improving muscle indices, although response rates appear to be influenced by baseline microbiota characteristics such as

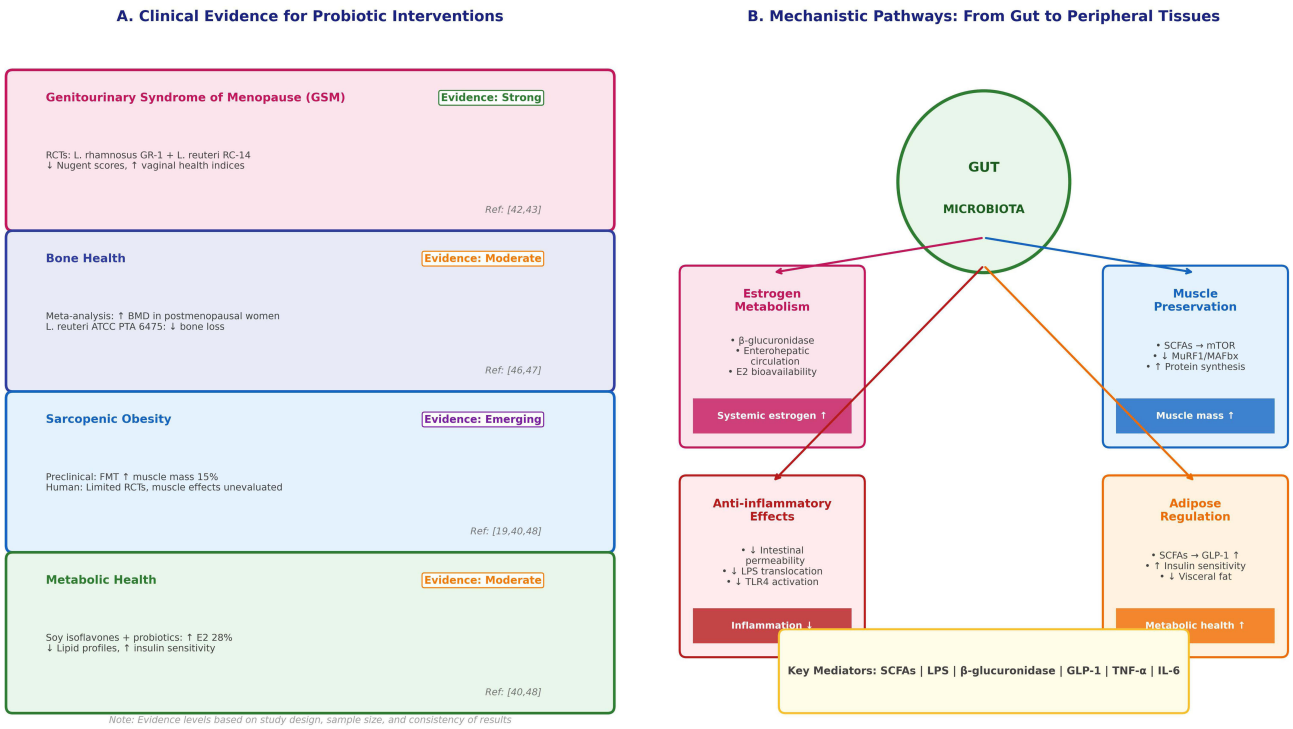

Figure 2 Clinical evidence and mechanistic pathways for probiotic interventions in menopausal women. (**A**) Evidence hierarchy across menopause-related conditions, from strong (GSM) to emerging (sarcopenic obesity). (**B**) Four primary mechanistic axes: estrogen metabolism, muscle preservation, anti-inflammatory effects, and adipose regulation.

equol-producing capacity.[40,48] Notably, substantial heterogeneity exists across studies in terms of strain selection, dosage, treatment duration, and outcome measures, limiting cross-study comparability.[52] Moreover, most trials lacked blinding or placebo controls, thus introducing potential placebo effects and publication bias.

Direct Associations Between Gut Microbiota and Skeletal Muscle Metabolism

Current evidence demonstrates that the gut microbiota can directly influence skeletal muscle function through immuno-metabolic pathways. At the mechanistic level, dysbiosis-associated elevation of lipopolysaccharide (LPS) can activate the TLR4 signaling pathway in skeletal muscle, promoting muscle protein degradation. A pivotal study by Doyle et al confirmed that LPS directly induces C2C12 myotube atrophy via TLR4, upregulating the expression of ubiquitin ligases MuRF1 and atrogin-1/MAFbx independent of systemic cytokine levels.[27] This LPS-TLR4-Muscle pathway has been validated in porcine models, where LPS directly upregulates muscle catabolic markers through the p38 MAPK and NF-κB pathways, leading to decreased skeletal muscle mass.[53] Conversely, microbial metabolites such as short-chain fatty acids (SCFAs) exhibit muscle-protective effects. Chambers et al demonstrated that targeted delivery of propionate to the colon via inulin-propionate ester significantly stimulates GLP-1 secretion and improves insulin sensitivity in overweight adults.[54] SCFAs increase GLP-1 secretion via FFAR2 and FFAR3 activation, thereby improving glucose tolerance and hepatic insulin sensitivity.[55] Although muscle mass was not directly assessed in these studies, the GLP-1 pathway was shown to augment muscle glucose uptake and protein synthesis. Population studies further support the microbiota-muscle axis. Hu et al conducted a metagenomic analysis of 1027 postmenopausal women, revealing that reduced gut microbiota alpha diversity significantly correlates with metabolic dysfunction, characterized by decreased Firmicutes/Bacteroidetes ratio and diminished Roseburia abundance.[16] Low microbiota diversity is associated with elevated systemic inflammatory markers (IL-6 and TNF-α),[56] which may impair muscle protein synthesis by inhibiting the PI3K/AKT/mTOR pathway,[57] ultimately contributing to muscle atrophy.[58] See Figure 3.

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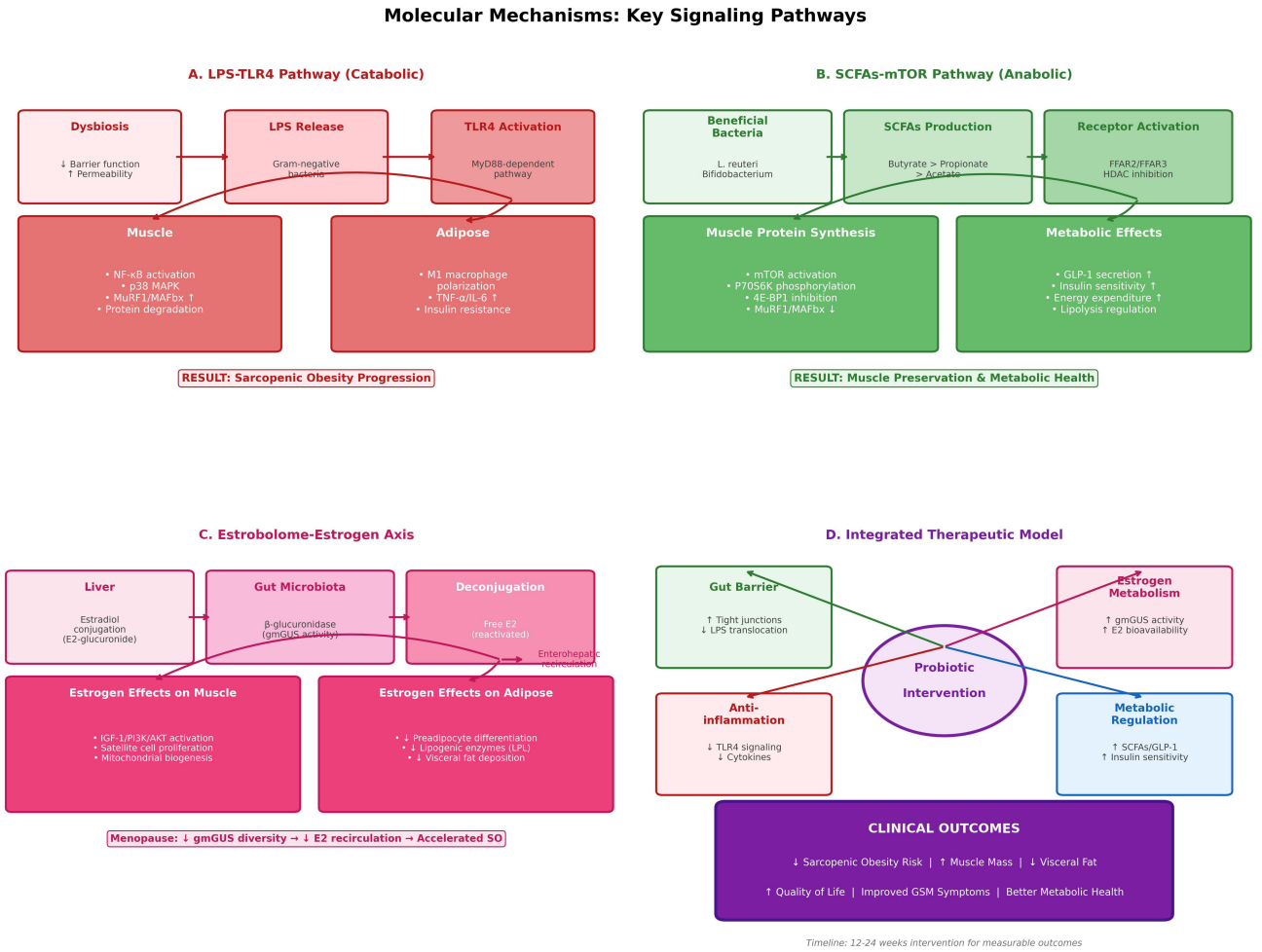

Figure 3 Molecular mechanisms of key signaling pathways. (**A**) LPS-TLR4 pathway: dysbiosis increases intestinal permeability, leading to muscle and adipose catabolism. (**B**) SCFAs-mTOR pathway: beneficial bacteria promote protein synthesis and metabolic health. (**C**) Estrobolome-estrogen axis: microbial β-glucuronidase enables estrogen recirculation, impaired in menopause. (**D**) Integrated therapeutic model: probiotics modulate multiple pathways to reduce sarcopenic obesity risk.

Integrated Studies on the Gut Microbiota-Estrogen-Muscle/Adipose Axis

The interplay between gut microbiota and estrogen may serve as a central hub in menopausal sarcopenic obesity. Peters et al performed a metagenomic analysis of the HCHS/SOL cohort and demonstrated that postmenopausal women exhibit a significantly lower abundance of β-glucuronidase (gmGUS) genes than premenopausal women, impairing estrogen enterohepatic circulation efficiency.[17] Intestinal microbes secrete β-glucuronidase to enhance estrogen reabsorption in enterohepatic circulation and mediate phytoestrogen metabolism, thereby regulating host estrogen homeostasis.[16] When this function is compromised post-menopause, systemic estrogen pools theoretically decrease, subsequently affecting muscle and adipose metabolisms. Estrogen deficiency exacerbates dysbiosis and adipose tissue dysfunction. Li et al demonstrated that estrogen-deficient environments activate visceral adipose macrophages through the LPS-TLR4 pathway, promoting IL-17 and RANKL secretion, and intensifying local inflammation.[59] This forms a mechanistic link with Doyle et al's 2011 muscle study, in which the same LPS-TLR4 pathway drives both adipose inflammation and muscle catabolism.[27] Estrogen signaling through ERα suppresses preadipocyte differentiation and expression of lipogenic enzymes, including LPL.[60] ERα-knockout mice exhibit adipocyte hyperplasia, hypertrophy, and insulin resistance.[61] Intervention studies have preliminarily explored the modifiability of this axis; however, the direct evidence remains limited. Preliminary data suggest that combined soy isoflavones and probiotics may improve lipid profiles; however, muscle parameters have not been evaluated in previous studies.[62] Evidence suggests that equol-producing capacity may influence phytoestrogen response, a metabolic capability conferred by specific gut strains (eg, Eggerthella spp)., although supporting evidence remains preliminary.[63] However, no study has directly assessed the effects of combined interventions on muscle mass or function in menopausal women, which represents a critical evidence gap. See Figure 4.

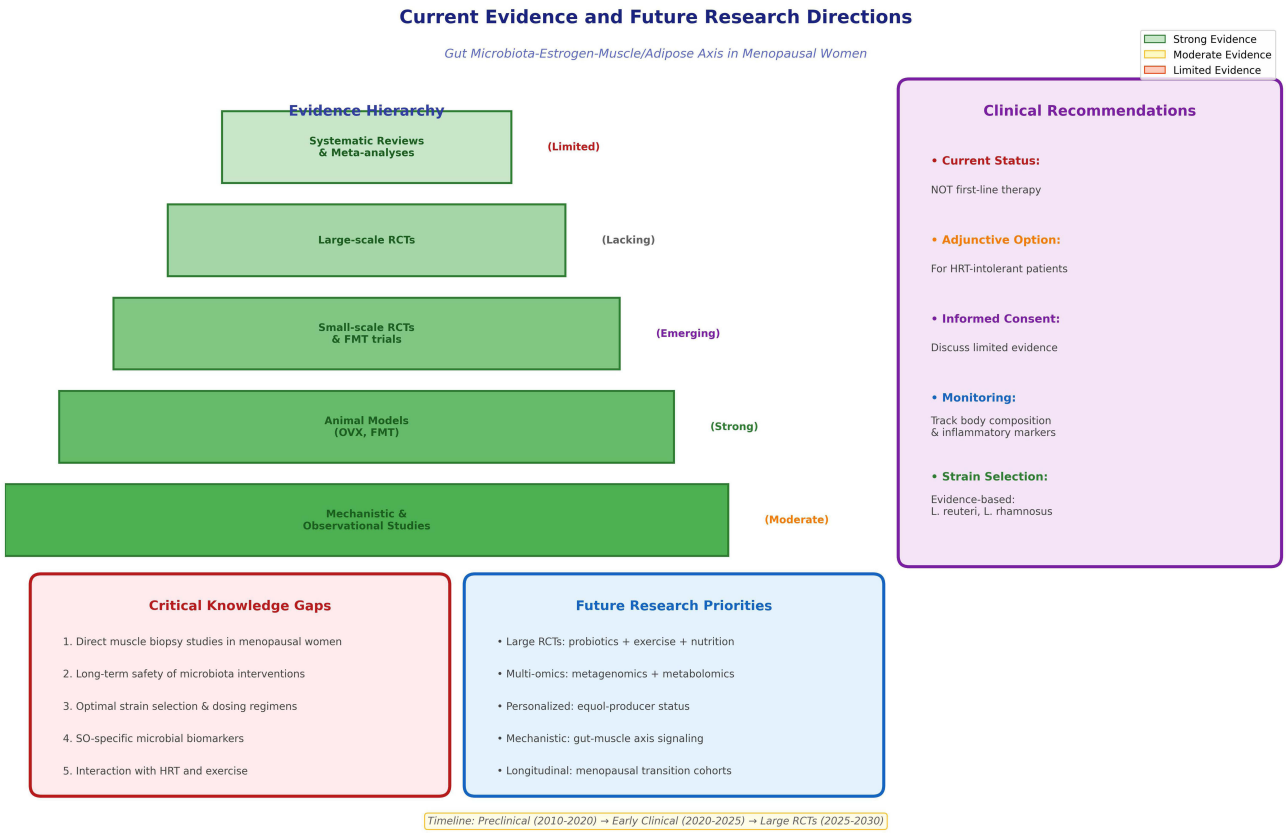

Figure 4 Current evidence hierarchy and future research directions. The pyramid illustrates strong preclinical data but limited large-scale RCTs. Key gaps include muscle biopsy studies, long-term safety, SO-specific biomarkers, and optimal strain selection. Future priorities emphasize personalized approaches, multi-omics, and combination interventions.

Conclusion

While mechanistic studies support the theoretical relevance of the gut microbiota-estrogen-muscle/adipose axis, clinical trials of microbiota interventions specifically targeting sarcopenic obesity populations are lacking. Current evidence does not support microbiota modulation as first-line therapy. For patients unwilling or unable to use conventional HRT, microbiota-targeted strategies may be considered adjunctive options with informed consent, pending future research to fill critical gaps: (1) prospective validation of SO-specific microbial biomarkers, (2) direct effects of microbiota interventions on muscle tissue, and (3) long-term safety data.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was funded by Zhejiang Traditional Chinese Medicine Science and Technology Plan Project; Construction Plan for the Inheritance Studio of Xiaoqing Jin Famous Chinese Medicine Expert in Zhejiang Province; Construction Plan for the Inheritance Studio of Xiaoqing Jin Famous Chinese Medicine Expert in China and “Pioneer” and “Leading Goose” R&D Program of Zhejiang. (grant nos. 2022ZB001, GZS2021011, 2022 NO. 75 and 2024C03208).

Disclosure

The authors have no conflicts of interest to declare in this work.

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