Can Probiotic Supplementation Improve Bone Mineral Density in Postmenopausal Women? A Systematic Review

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Abstract

Background: Postmenopausal women face a high risk of osteoporosis, often necessitating long-term management strategies beyond conventional pharmacological treatments. The emerging "gut-bone axis" theory suggests that gut microbiota significantly influences bone metabolism, positioning probiotic supplementation as a potential novel intervention for bone health.

Aim: This systematic review aims to evaluate the effects of probiotic supplementation on total hip and lumbar spine bone mineral density (BMD) in postmenopausal women.

Methods: We searched PubMed, Web of Science, and the Cochrane Library databases for relevant randomized controlled trials (RCTs) from their inception to November 2025. Study quality was assessed using the Cochrane risk of bias tool. Data were pooled using standardized mean differences (SMD) with 95% confidence intervals (CIs) in a random-effects model, and heterogeneity was quantified using the I^2 statistic.

Summary: Four RCTs involving 461 postmenopausal women were included. The pooled analysis showed a non-significant positive trend for both total hip BMD (SMD = 0.60, 95% CI: -0.17 to 1.38) and lumbar spine BMD (SMD = 0.48, 95% CI: -0.03 to 1.00), with considerable heterogeneity (I^2 = 95% and 89%, respectively). Current evidence suggests a potential beneficial effect of probiotics on BMD, likely mediated through gut microbiota regulation, estrogen metabolism, and inflammatory modulation. However, the conclusions are limited by the small number of studies, high heterogeneity, and varying intervention protocols. Future large-scale, long-term RCTs with standardized protocols are warranted to confirm these findings and elucidate optimal probiotic strategies.

Keywords: Probiotics, Postmenopausal Women, Osteoporosis, Systematic Review, Gut-bone Axis.

Introduction

Research Background

Osteoporosis (OP) is a common metabolic bone disorder characterized by reduced bone mass and impaired bone microarchitecture, leading to increased bone fragility and elevated fracture risk [1]. This disease is categorized into primary and secondary types: primary OP arises from aging and estrogen deficiency, while secondary OP results from underlying diseases or medications [2]. Postmenopausal women face heightened OP risk due to aging and hormonal imbalances disrupting the equilibrium between bone formation and resorption. Among primary osteoporosis, postmenopausal osteoporosis (PMOP) is the most prevalent form [3].

Current clinical management of PMOP primarily relies on bisphosphonates and estrogen replacement therapy. However, long-term use of these medications may induce adverse effects such as poor fracture outcomes and increased cancer risk [4, 5]. Therefore, exploring safe, effective, and well-tolerated supplementary interventions holds significant clinical importance.

In recent years, the emergence of the "gut-bone axis" theory has opened new perspectives for osteoporosis prevention and treatment [6]. As the largest microbial ecosystem in the human body, alterations in the structure and function of the gut microbiota are closely linked to skeletal health [7]. Probiotics, as key mediators regulating the gut microbiota, may profoundly influence bone metabolism through pathways including improving the intestinal microenvironment, modulating immune-inflammatory responses, and affecting nutrient absorption and hormone metabolism [8, 9]. Existing research suggests probiotic supplementation may hold potential for enhancing bone density and improving bone metabolism, but systematic evidence-based medical data regarding its effects in postmenopausal women remains lacking [10].

Research Objectives
This study aims to synthesize existing randomized controlled trial evidence to examine the effects of probiotic supplementation on lumbar spine and total hip bone mineral density in postmenopausal women, providing scientific basis for clinical interventions and future research on PMOP.

Research Significance
Further elucidate the mechanism of the "gut-bone axis" in postmenopausal women, enriching the theoretical framework of osteoporosis pathogenesis. To offer a potentially safe, effective, and cost-effective supplemental intervention for postmenopausal women with osteoporosis, providing evidence-based support for clinical decision-making.

Methods
Literature Search Strategy
Databases including PubMed, Web of Science, and Cochrane Library were searched from their inception to November 2025. Search terms combined subject headings with free-text keywords, including "probiotics," "postmenopausal women," "osteoporosis," "bone mineral density," "randomized controlled trial," and "gastrointestinal microbiomes." References from included studies were manually searched to supplement potentially overlooked literature.

Inclusion and Exclusion Criteria for Literature
Inclusion and exclusion criteria were strictly defined according to the PICOS framework (P: population; I: intervention; C: comparison; O: outcome; S: study design) (Table 1).

Table 1: PICOS framework for the study

Population (P)	postmenopausal women
Intervention (I)	probiotics
Comparison (C)	•Placebo intervention
	•Sham intervention
Outcomes (O)	•Lumbar spine BMD
	•Total hip BMD
	•Gut microbiota
	•Adverse events
Study Design(S)	RCT

Inclusion Criteria:
- **Study type**: Randomized controlled trial (RCT);
- **Study population**: Postmenopausal women;
- **Intervention**: Probiotic supplementation (with specified strains, dosage, and duration); •control group: placebo or standard care;
- **Outcome measures**: Changes in total hip or lumbar spine bone mineral density (BMD).

Exclusion Criteria:
- Non-RCT studies (e.g., cohort studies, case-control studies);
- Inclusion of male subjects or premenopausal women;
- Absence of bone mineral density data or inability to extract such data;
- Duplicate publications;
- Interventions combining probiotics with other osteoporosis medications, precluding separate analysis of probiotic effects.

Literature Screening and Data Extraction
Two researchers independently screened titles, abstracts, and full texts, cross-verifying results. Disagreements were resolved through discussion or third-party consultation.

Risk of Bias Assessment
The Cochrane Risk of Bias tool was used to assess study quality across seven domains:
1. Random sequence generation (selection bias);
2. Allocation concealment (selection bias);
3. Blinding of participants and personnel (performance bias);
4. Blinding of outcome assessment (detection bias);
5. Completeness of outcome data (attrition bias);
6. Selective reporting (reporting bias);
7. Other biases.

Risk levels for each domain are categorized as low risk (green), unclear (yellow), or high risk (red).

Statistical Analysis
Literature quality assessment was conducted using Revman software, with analysis performed in R software. Standardized mean difference (SMD) and 95% confidence interval (CI) were used as effect size measures. Heterogeneity was assessed using the I^2 statistic. A random-effects model was applied if high heterogeneity was present; otherwise, a fixed-effects model was used.

Results
Literature Search Findings
A systematic search of PubMed, Web of Science, and the Cochrane Library yielded 617 initial records. After removing duplicates, 221 articles proceeded to screening. Initial title and abstract screening excluded 159 articles that did not meet the criteria. Full-text reviews of the remaining 62 studies led to the exclusion of 58 studies, primarily due to: lack of detailed data (n=27), discussion of unrelated topics (n=19), and non-compliance with study design or exposure criteria (n=12). Ultimately, four randomized controlled trials (RCTs) were included in this systematic review. The study inclusion flowchart is shown in Figure 1.

Figure 1: Flow chart of study selection for inclusion in the systematic review
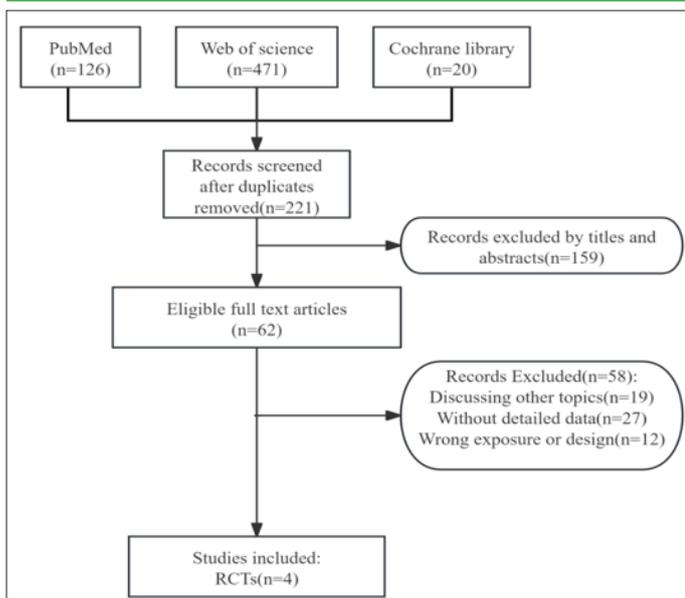
Basic Characteristics of Included Studies

The four included studies involved a total of 461 postmenopausal female participants, comprising 235 in the treatment group and 226 in the control group. Intervention durations ranged from 12 weeks to 12 months, with probiotic strains including common species such as Lactobacillus (e.g., Lactobacillus acidophilus, Lactobacillus casei) and Bifidobacterium (e.g., Bifidobacterium lactis). Specific characteristics are summarized in Table 2.

Table 2: Summary of studies

Author,	study design	Country	Study	Type of intervention		Subjects		Outcome measures
Year			duration	Trial Group	Control Group	Trial Group	Control Group	
Nillsson, 2018[11]	RCT	Sweden	12 months	Freeze-dried L. reuteri 6475 in	Consisted of	45	45	BMD
				doses of 5 × 109 (CFU) mixed				BALP, CRP
				along with maltodextrin				TNF-α, a, NTx
				powder taken twice daily,				Adverse events
				yielding a total daily dose of				
				1 × 1010 CFU day_1				
Takimoto, 2018[12]	RCT	Japan	24 weeks	Dried soybeans fermented	Tablets containing	38	38	BMD, TRACP-5b
				using a pre-culture prepared	dextrin instead of the			BAP, PTH
				from soybean oil residue	soybean fermentation			Gut microbiota analysis
				inoculated with Bacillus	extract			
				subtilis (C-3102)				

Han, 2022[13]	RCT	Korea	6 months	Probiotics capsule (L.	Capsule	30	28	BMD, CTX +OC, BALP
				fermentum SRK414,	microcrystalline			ALP, 25(OH)D
				4.0 × 109 CFU)	cellulose) twice a day			Gut microbiota
								concentration
								Adverse events
Schott, 2025[14]	RCT	Australia	6/12 months	SBD111 synbiotic medical food,	Capsule Consisted of	122/115	115/105	BMD, CTX
				vitaminD (500 IU)	maltodextrin powder			BALP, CRP
					vitaminD(500 IU)			TNF-α, IL-1β
								RANKL, IL-4
								Adverse events

Risk of Bias Assessment

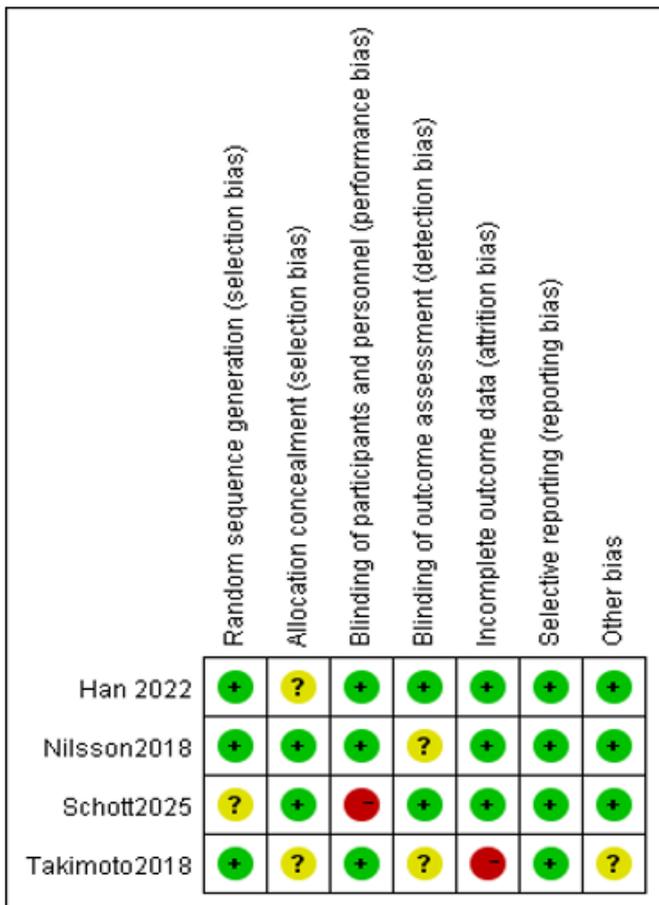Risk of bias assessments for the included studies are presented in Figure 2.

Figure 2: Risk assessment scale of studies.

Analysis Results

Changes in Lumbar Spine BMD

A meta-analysis was conducted on four randomized controlled trials evaluating changes in lumbar spine bone mineral density (BMD). Results from each study are presented in Figure 3. The analysis revealed conflicting findings across studies. Two studies (Nilsson, 2018; Takimoto, 2018) demonstrated positive effects of the interventions (SMDs of 0.57 and 1.96, respectively), while the remaining studies (Han, 2022; Schott, 2025) observed no effect (all SMD 95% confidence intervals included zero). High heterogeneity existed among studies ($I^2 = 89\%$, $\tau^2 = 0.3005$, $p < 0.0001$) [11-14].
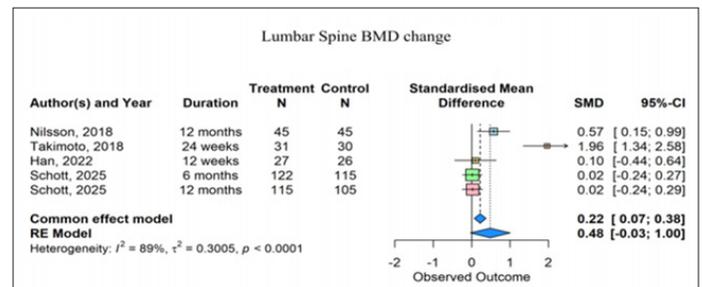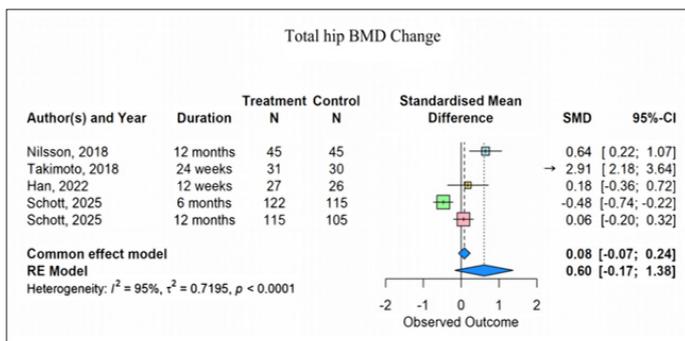

Figure 3: Forest plot of probiotics supplements on lumbar spine BMD

Changes in Total Hip BMD

This study conducted a meta-analysis of randomized controlled trials evaluating changes in total hip bone mineral density (BMD). Results from individual studies are shown in Figure 4. Analysis revealed divergent outcomes across studies. Takimoto 2018 reported a positive effect (SMD = 2.91), whereas Han 2022 demonstrated a negative effect (SMD = -2.91) [12,13]. The direction and magnitude of results from other studies were also inconsistent. Extremely high heterogeneity existed between studies ($I^2 = 95\%$, $\tau^2 = 0.7195$, $p < 0.0001$). The pooled effect size from the random-effects model was not statistically significant (SMD = 0.60, 95% CI: -0.17 to 1.38).

Figure 4: Forest plot of probiotics supplements on hip BMD

Discussion

Effects of Probiotics on Bone Mineral Density in Postmenopausal Women

Our findings indicate that while the pooled effect size for probiotic supplementation on changes in total hip and lumbar spine BMD was positive, the difference was not statistically significant due to high heterogeneity. This partially aligns with previous meta-analysis results in postmenopausal women.

### Analysis of Sources of Heterogeneity

The high heterogeneity observed in this study may stem from the following sources:

Differences in study population characteristics: Included postmenopausal women varied in age, duration since menopause, baseline bone density, and BMI. Variations in probiotic intervention protocols: Differences existed in probiotic strains (e.g., Lactobacillus spp., Bifidobacterium spp.), dosage, intervention duration, and whether prebiotics were co-administered. Different strains may influence bone health through distinct metabolic pathways, while varying intervention durations could also lead to differences in effect sizes.

Differences in outcome measurement methods: Although dual-energy X-ray absorptiometry (DXA) was used to measure bone density across studies, subtle variations in imaging equipment, site selection, and operational standards may have contributed to heterogeneity.

Exploring Mechanisms: The Unique Association Between the Gut-Bone Axis and Postmenopausal Women

In postmenopausal women, the mechanisms underlying the gut-bone axis may be more complex, as illustrated in Figure 5.
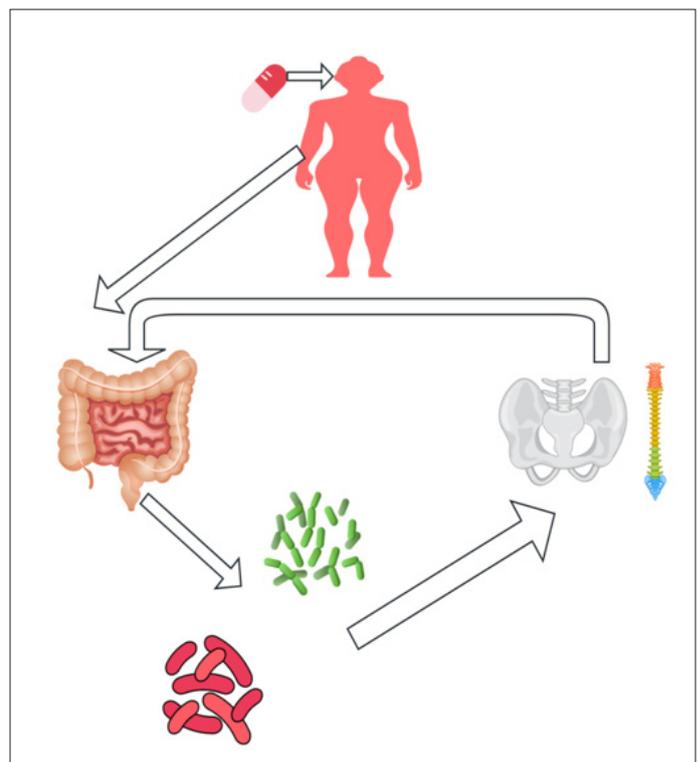
Figure 5: Gut-bone axis Schematic Diagram

Bidirectional Regulation Between Gut Microbiota and Estrogen Metabolism

Postmenopausal women experience a sharp decline in estrogen levels, leading to alterations in gut microbiota composition. Beneficial bacteria such as Bifidobacteria and Lactobacillus decrease in abundance, while potentially pathogenic bacteria increase [15,16]. Concurrently, gut microbiota can influence estrogen levels through metabolic processes [17].

Regulation of Gut Microbiota and Inflammatory Responses

Declining estrogen levels in postmenopausal women exacerbates inflammatory responses. Chronic low-grade inflammation promotes osteoclast activity and accelerates bone loss [18]. Probiotics can modulate gut microbiota to reduce production of pro-inflammatory factors (e.g., IL-6, TNF-α) while increasing secretion of anti-inflammatory factors (e.g., IL-10), thereby inhibiting inflammation-mediated bone resorption [19, 20].

Improvement of Gut Microbiota and Nutrient Absorption

Probiotics enhance intestinal barrier function, promoting absorption of bone-health-related nutrients like calcium and vitamin D. Vitamin D deficiency is common among postmenopausal women, and probiotics may increase vitamin D bioavailability by modulating gut microbiota, thereby enhancing calcium absorption [21].

Study Limitations

Limited number of included studies: Only four RCTs were included, with relatively small sample sizes potentially affecting statistical power. Variable study quality: Some studies carried risks of allocation concealment and blinding implementation, potentially introducing bias. Lack of Subgroup Analysis by Probiotic Strain and Dose: Due to significant variations in intervention protocols across included studies, detailed subgroup

analyses were not feasible, making it difficult to determine the optimal probiotic strain or dosage. Short Follow-up Duration: Most studies had follow-up periods of less than 12 months, lacking long-term data to assess the sustained efficacy and safety of probiotics.

Conclusions and Outlook
Conclusions
Current evidence suggests that probiotic supplementation may positively influence bone mineral density in postmenopausal women with osteoporosis. Its mechanisms of action are likely closely related to regulating gut microbiota, improving estrogen metabolism, suppressing inflammatory responses, and promoting nutrient absorption. However, due to the limited number of included studies and high heterogeneity, these conclusions require further validation.

Future Directions
Conduct large-scale, multicenter, long-term follow-up randomized controlled trials (RCTs) with standardized intervention protocols (including probiotic strains, dosage, and intervention duration) and outcome assessment criteria to enhance study reliability and comparability. Further explore the specific molecular mechanisms of the gut-bone axis in postmenopausal women to clarify the target sites of different probiotic strains. Investigate the combined effects of probiotics with other osteoporosis therapies (such as bisphosphonates and estrogen replacement therapy), evaluating their synergistic effects and safety.

Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Declaration of Generative AI and AI-assisted Technologies in the Manuscript Preparation Process
During preparation of this work, we used DeepSeek in order to help with writing in English. After using this service, we reviewed and edited the content as needed and take full responsibility for the content of the published article.

Reference
1. Juliet E Compston, Michael R McClung, William D Leslie (2019) Osteoporosis Lancet 393: 364-376. https://doi.org/10.1016/s0140-6736(18)32112-3.
2. Cara Tannenbaum, Julie Clark, Kevin Schwartzman, Sylvan Wallenstein, Robert Lapinski, et al. (2002) Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. J Clin Endocrinol Metab 87: 4431-4437.
3. Marcella Donovan Walker, Elizabeth Shane (2023) Postmenopausal Osteoporosis. N Engl J Med 389: 1979-1991.
4. Stephen L Kates, Cheryl L Ackert-Bicknel (2016) How do bisphosphonates affect fracture healing? Injury 47: S65-68.
5. Lorusso L, Pieruzzi L, Gabriele M, Nisi M, Viola D, et al. (2021) Osteonecrosis of the jaw: a rare but possible side effect in thyroid cancer patients treated with tyrosine-kinase inhibitors and bisphosphonates. J Endocrinol Invest 44: 2557-2566.
6. Hugo S Pereira, Muaz Rashid, Ahmad Alissa, Salman Keraidi, Nicolas Wipf, et al. (2025) Exploring Oste microbiology: A narrative review of the gut-bone axis in osteoporosis. Ir J Med Sci 194: 2265-2274.
7. Macy Castaneda, Kelsey Smith, Jacob C Nixon, Christopher J Hernandez, Sheldon Rowan (2021) Alterations to the gut microbiome impair bone tissue strength in aged mice. Bone Rep 14: 101065.
8. Rémy Burcelin (2016) Gut microbiota and immune crosstalk in metabolic disease. Mol Metab 5: 771-781.
9. Sébastien Lucas, Yasunori Omata, Jörg Hofmann, Martin Böttcher, Aida Iljazovic, et al. (2018) Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. Nat Commun 9: 55.
10. Kevin D Seely, Cody A Kotelko, Hannah Douglas, Brandon Bealer, Amanda E Brooks (2021) The Human Gut Microbiota: A Key Mediator of Osteoporosis and Osteogenesis. Int J Mol Sci 22: 9452.
11. Nilsson AG, Sundh D, Bäckhed F, Lorentzon M (2018) Lactobacillus reuteri reduces bone loss in older women with low bone mineral density: a randomized, placebo-controlled, double-blind, clinical trial. J Intern Med 284: 307-317.
12. Takuou Takimoto, Misaki Hatanaka, Tomohiro Hoshino, Tsuyoshi Takara, Ko Tanaka, et al. (2018) Effect of Bacillus subtilis C-3102 on bone mineral density in healthy postmenopausal Japanese women: a randomized, placebo-controlled, double-blind clinical trial. Biosci Microbiota Food Health 37: 87-96.
13. Hee Soo Han, Jung Geul Kim, Yoon Hyo Choi, Kyoung Min Lee, Tae Hun Kwon, et al. (2022) Effect of Lactobacillus Fermentum as a Probiotic Agent on Bone Health in Postmenopausal Women. J Bone Metab 29: 225-233.
14. Eric M Schott, Mark R Charbonneau, Douglas P Kiel, Susan Bukata, Michael J Zuscik, et al. (2025) A randomized, double-blind, placebo-controlled clinical study to evaluate the efficacy of the synbiotic medical food, SBD111, for the clinical dietary management of bone loss in menopausal women. Osteoporos Int 36: 2019-2030.
15. Maryann Kwa, Claudia S Plottel, Martin J Blaser, Sylvia Adams (2016) The Intestinal Microbiome and Estrogen Receptor-Positive Female Breast Cancer. J Natl Cancer Inst 108: djw029.
16. Juneyoung Lee, Pedram Peesh, Victoria Quaicoe, Chunfeng Tan, Anik Banerjee, et al. (2023) Estradiol mediates colonic epithelial protection in aged mice after stroke and is associated with shifts in the gut microbiome. Gut Microbes 15: 2271629.
17. Xinyu Qi, Chuyu Yun, Yanli Pang, Jie Qiao (2021) The impact of the gut microbiota on the reproductive and metabolic endocrine system. Gut Microbes 13: 1- 21.
18. Shadi S Yarandi, Daniel A Peterson, Glen J Treisman, Timothy H Moran, Pankaj J Pasricha (2016) Modulatory

Effects of Gut Microbiota on the Central Nervous System: How Gut Could Play a Role in Neuropsychiatric Health and Diseases. J Neurogastroenterol Motil 22: 201-212.

19. Lisa Rizzetto, Francesca Fava, Kieran M Tuohy, Carlo Selmi (2018) Connecting the immune system, systemic chronic inflammation and the gut microbiome: The role of sex. J Autoimmun 92: 12-34.

20. Kendra Hodgkinson, Faiha El Abbar, Peter Dobranowski, Juliana Manoogian, James Butcher, et al. (2023) Butyrate's role in human health and the current progress towards its clinical application to treat gastrointestinal disease. Clin Nutr 42: 61-75.

21. John H White (2022) Emerging Roles of Vitamin D-Induced Antimicrobial Peptides in Antiviral Innate Immunity. Nutrients 14: 284.