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REVIEW

Beyond Hormone Replacement: Multifaceted Effects of Phytoestrogens for Optimizing Kinesiological and Physiological Adaptations in Postmenopausal Women

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Abstract: Phytoestrogens (PEs), a class of naturally occurring plant compounds primarily categorized into isoflavones, lignans, flavonoids, coumarins, and stilbenes, exhibit structural similarity to endogenous estrogens and exert regulatory effects through estrogen receptors. This comprehensive review examines the multifaceted roles of PEs in enhancing exercise performance and promoting health among postmenopausal women. Current evidence demonstrates that PEs not only ameliorate characteristic menopausal symptoms but, more significantly, improve physical function through multiple mechanisms: (1) augmenting muscle protein synthesis while mitigating inflammation and oxidative stress to optimize muscular performance; (2) modulating glucolipid metabolism and cardiovascular function to establish physiological foundations for exercise; and (3) preserving bone mineral density and regulating neurotransmitter activity to maintain motor coordination. Although combined PE-exercise interventions demonstrate synergistic benefits, their efficacy is influenced by dosage variations and interindividual metabolic differences. Future investigations should prioritize the development of precision PE applications to optimize kinesiological outcomes and health parameters in postmenopausal populations.

Keywords: phytoestrogens, elderly, exercise performance, physical activity, menopausal symptoms

Introduction

Menopausal syndrome (MPS), sometimes referred to as menopausal symptoms, refers to a cluster of symptoms arising in women around the time of menopause due to dysregulation of the hypothalamic-pituitary-ovarian axis, leading to a rapid decline in endogenous estrogen levels.[1] With increasing global life expectancy, over one-third of postmenopausal women spend their lives in a state of chronic estrogen deficiency. It is projected that by 2030, the female population in China experiencing menopause and postmenopause will reach 210 million, with more than 85% potentially experiencing varying degrees of menopausal symptoms;[2] worldwide, this demographic is expected to grow to 1.2 billion, with approximately 47 million new cases annually.[3]

Phytoestrogens (PEs) are a class of naturally occurring plant-derived compounds exhibiting estrogenic activity. Structurally like 17β-estradiol, they can competitively bind to estrogen receptors, exerting selective tissue modulation effects. Based on chemical structure, PEs are primarily classified into isoflavones (eg, genistein, daidzein), lignans (eg, secoisolariciresinol), flavonoids, coumarins (eg, coumestrol), and stilbenes (eg, resveratrol). Variations exist in metabolism and bioactivity among different subclasses and within the same class. Given concerns regarding the potential risks associated with hormone replacement therapy (HRT), PEs have garnered attention for their estrogen-like effects and relative safety, demonstrating benefits in alleviating vasomotor symptoms, maintaining bone mineral density, and modulating lipid metabolism in postmenopausal women.[4–6]

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Beyond typical menopausal symptoms, estrogen deficiency significantly impacts physical function, exercise performance, and quality of life by accelerating sarcopenia, reducing bone density, impairing endurance and balance, and delaying recovery from physical activity.[7,8] However, the effects of PEs on specific physical performance indicators such as strength and endurance, as well as physiological adaptations induced by exercise training—encompassing musculoskeletal, cardiovascular, and nervous system responses—remain insufficiently studied and systematically organized. As a potential alternative or adjunctive strategy, PEs are increasingly recognized for their role in alleviating menopausal symptoms and potentially maintaining or enhancing physical capacity and physiological adaptability. Optimizing exercise interventions to improve quality of life, health management, and reduce the incidence of MPS constitutes a pressing public health challenge.

This review aims to systematically synthesize the current evidence regarding the effects of PEs alone or in combination with exercise training on physical performance and underlying physiological adaptations in postmenopausal women. It critically evaluates the potential influence of PEs on exercise training adaptation and recovery processes, identifies existing knowledge gaps, and provides a scientific basis for developing PE-based exercise intervention strategies to enhance physiological functions and exercise capacity in this population.

Literature Search Methodology

This study employs a narrative review methodology, retrieving literature published between 2001 and 2025 from PubMed, Web of Science, and China National Knowledge Infrastructure (CNKI) databases. The search keywords include "phytoestrogens", "postmenopausal women", "menopause", "lignans", "isoflavones", "exercise", "physical activity", "muscle strength", and combinations with terms such as "clinical trial" and "mechanism". Inclusion criteria encompass original research articles or meta-analyses involving human subjects or relevant animal models, published in both Chinese and English. Exclusion criteria include reviews, conference abstracts, and low-quality studies lacking control groups. A total of 138 articles were selected, with a focus on high-evidence-level studies such as randomized controlled trials and mechanistic investigations for comprehensive analysis.

Phytoestrogens and Menopausal Syndrome

Major Symptoms of Menopausal Syndrome

According to the World Health Organization (WHO), the average age of natural menopause globally ranges from 45 to 55 years.[9] Approximately 80% of women experience typical menopausal symptoms, primarily vasomotor disturbances such as hot flashes and night sweats;[10] neurocognitive issues including anxiety and depression;[11] and cardiovascular-metabolic abnormalities characterized by elevated total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C).[12] These physiological changes significantly impair quality of life and predispose women to multidimensional declines in physical function,[13] including neuromuscular weakening,[14] reduced maximal oxygen uptake (VO2max),[15] and increased incidence of osteoarthritis,[16] thereby creating a vicious cycle of "metabolic-physical function" deterioration. These pathological alterations are positively correlated with increased risks of chronic diseases in old age.

PEs as a Therapeutic Modality for Menopausal Symptoms

Hormone replacement therapy (HRT) remains the conventional treatment for menopausal syndrome. Initiation of HRT before or after menopause confers primary prevention benefits against osteoporotic fractures.[17] However, prolonged HRT use may adversely affect the nervous system, especially when estrogen is administered alone. Morrison et al conducted a randomized controlled trial (RCT) demonstrating that estrogen therapy was ineffective in treating mild to moderate depression in menopausal women, with progesterone supplementation showing no significant improvement in depressive symptoms.[18] From a safety perspective, patients requiring long-term HRT should actively explore alternative strategies that harness estrogenic effects while minimizing potential adverse reactions.

In contrast, PEs, as naturally occurring plant-derived estrogens, exert physiological effects through differential activation of estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ). They can mimic endogenous estrogen, reduce lipid levels, and demonstrate significant potential in lowering the risk of coronary heart disease (CHD).[19] The

British Menopause Society recommends that low-dose natural PEs be used to treat menopausal symptoms, with minimal risk of venous thromboembolism,[20] thus providing a safer management option for menopausal syndrome.

Common Types of PEs and Their Roles in Menopausal Symptom Relief

Isoflavones (ISO)

Isoflavones are a class of PEs predominantly found in leguminous plants, with active forms including daidzein, genistein, and puerarin.[21–23] Soybeans and their products—such as tofu, soy milk, and natto—serve as high-quality dietary sources, containing approximately 128 milligrams of isoflavones per 100 grams of soybeans.[24] The consumption of legume-based diets is widespread across Asia, with traditional Japanese dietary patterns exemplifying this trend.[25]

Multiple studies have demonstrated that soybean isoflavones can significantly reduce the frequency and severity of hot flashes and alleviate symptoms such as night sweats.[26,27] Their mechanism of action may involve mimicking estrogenic activity and modulating estrogen receptor activity, potentially reducing the risk of hormone-dependent cancers, including cervical, breast, and prostate cancers.[28–32] It is noteworthy that the bioavailability of isoflavones is influenced by gut microbiota metabolism,[33] and the synergistic effects of isoflavones with physical activity interventions, such as resistance training, warrant further investigation.

Lignans

Lignans are a class of polyphenolic compounds widely distributed in plants, with flaxseed being the richest dietary source, containing up to 53,000 micrograms per 100 grams.[34] Gut microbiota metabolize lignans into enterolactone, a compound structurally similar to estrogen, conferring a unique bidirectional regulatory capacity: alleviating menopausal symptoms while acting as antagonists in high-estrogen environments.[35,36]

In cardiovascular health, specific lignans such as matairesinol have been shown to improve endothelial function,[37] while the intake of lariciresinol is associated with a 30% reduction in the risk of hypercholesterolemia.[38] Clinical evidence indicates that flaxseed consumption can significantly lower total cholesterol levels in postmenopausal women,[39] and lignans in sesame oil exert protective effects through modulation of lipid metabolism.[40] Regarding metabolic health, the metabolite enterolactone correlates with a reduced risk of type 2 diabetes, particularly among obese individuals and postmenopausal women.[41]

However, the health effects of lignans exhibit considerable individual variability. Western populations, which consume higher amounts of flaxseed and sesame, tend to have greater lignan intake compared to Eastern populations.[42] Some individuals lack key metabolic enzymes necessary for efficient conversion of lignans into bioactive forms, a process closely linked to gut microbiota composition and metabolic capacity.[43] Personalized intervention strategies should account for these differences.

Flavonoids

Flavonoids are a widespread class of polyphenolic compounds in plants, exhibiting notable value in menopausal health management. These compounds possess significant anti-inflammatory and antioxidant properties,[44,45] with representative constituents such as apigenin and quercetin demonstrating phytoestrogenic activity.

Apigenin is distinguished by its potent antioxidant capacity, prevalent in temperate fruits and vegetables, effectively scavenging free radicals and reducing oxidative stress-induced damage.[46] Quercetin offers broader health benefits, including improvements in glycemic and lipid profiles,[47] and exhibits multi-target therapeutic potential in breast cancer prevention and treatment.[48] Animal studies have confirmed that quercetin supplementation can markedly improve metabolic parameters and enhance antioxidant enzyme activity in ovariectomized rat models.[49]

It is important to note that, despite the presence of flavonoids in common foods such as apples and broccoli, their health benefits remain subject to debate. For instance, flavonoid intake has not been consistently associated with a reduced risk of cancer.[50] While chocolate, a flavonoid-rich processed food, can improve arterial stiffness, its effects on vascular structure are limited.[51] These discrepancies underscore the importance of considering flavonoid types and individual characteristics when evaluating their health impacts.

Coumarins

Coumarin compounds are a class of naturally occurring substances characterized by distinctive aromatic properties, demonstrating multifaceted applications in the maintenance of health among menopausal women. The core structure of these compounds is benzopyranone, which can be subdivided into various types, such as simple coumarins and furanocoumarins, based on different substituents.

In the field of exercise physiology, coumarins exert significant vasodilatory effects that enhance blood circulation,[52] which is particularly beneficial for menopausal women engaging in aerobic activities, thereby improving cardiopulmonary function and alleviating exercise-induced fatigue. Regarding oncological prevention and treatment, specific coumarin derivatives act through targeting the HDAC1-Sp1-FOSL2 signaling axis or by inhibiting NUDT5,[53,54] thereby exerting anti-breast cancer effects. Additionally, 7,8-dihydroxy-4-methylcoumarin (DHMC) not only reduces fasting blood glucose levels but also exhibits notable anxiolytic properties,[55] offering potential solutions for common menopausal issues.

Stilbenes

Stilbene compounds are vital secondary metabolites produced by plants to defend against environmental stressors,[56] with high concentrations found in grapes, peanuts, and Polygonum multiflorum.[57,58] Among these, resveratrol is the most representative, distinguished by its excellent antioxidant and anti-inflammatory properties, which are prominent in supporting menopausal health.[59] In cancer prevention, multiple stilbenes derived from muscat grapes demonstrate synergistic effects against triple-negative breast cancer cells that surpass those of resveratrol alone.[60,61] In the context of exercise health, clinical studies confirm that resveratrol supplementation effectively reduces exercise-induced muscle damage and enhances athletic performance, which is significant for improving physical capacity in menopausal women.[62] These findings suggest that stilbene compounds may serve as effective adjuncts in the health management of menopausal women.

Absorption and Utilization Mechanisms of PEs in the Human Body

PEs are naturally occurring plant secondary metabolites structurally and functionally like mammalian estrogens, exhibiting diverse biological activities. Compared to endogenous estrogens such as 17β-estradiol, PEs are ingested via the gastrointestinal tract and undergo complex processes including digestion, absorption, metabolism, distribution, binding, and excretion. The absorption and utilization of PEs constitute a dynamic, multi-step regulatory process, with their ultimate biological effects dependent on intricate interactions among the host, microbiota, and diet.

Endogenous estrogens, notably 17β-estradiol, are highly active, characterized by a tetracyclic structure comprising rings A, B, C, and D, with ring A containing a phenolic hydroxyl group. The chemical similarity between PEs and endogenous estrogens enables PEs to bind to estrogen receptors ERα and ERβ, thereby exhibiting estrogen-like biological activity (Figure 1). For instance, the A and C rings of isoflavone-type PEs resemble the A and D rings of 17-β-estradiol, both containing phenolic hydroxyl groups; lignan and coumarin derivatives feature phenyl rings and hydroxyl groups structurally similar to those in endogenous estrogens.

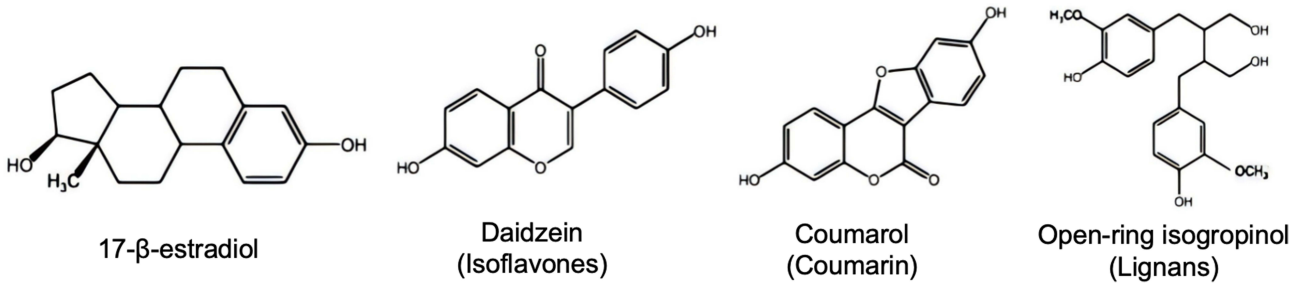

Figure 1 Structural formula of 17-β-estradiol and representative PEs.

The bioavailability of PEs is jointly regulated by their chemical structure, metabolic transformation, and individual host factors. The absorption and utilization process can be delineated into key stages: initial breakdown and absorption in the gastrointestinal tract; subsequent microbial metabolism that releases active constituents into the bloodstream; and finally, binding to estrogen receptors to exert biological effects.

Absorption, Distribution, and Metabolism

PEs predominantly exist in plants in the form of glycosides. Upon oral ingestion, β-glucosidases present in gastric acid and the intestinal tract hydrolyze glycosidic bonds, releasing bioactive aglycones. For example, in isoflavone-rich PEs, the soy aglycone can be metabolized by gut microbiota into more potent metabolites such as equol (Figure 2). Similarly, lignan-type PEs, including matairesinol and seco-isolariciresinol, are converted by intestinal bacteria into enterodiol and enterolactone (Figure 3), which exhibit enhanced antioxidant activity and biological effects.

Subsequently, free aglycones traverse the intestinal epithelium via passive diffusion or active transport mechanisms, then enter the portal circulation to reach the liver. They undergo Phase I metabolism (oxidation, reduction, hydrolysis)

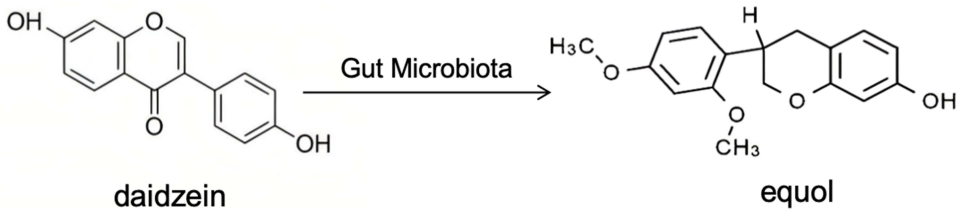

Figure 2 Absorption and metabolism of daidzein.

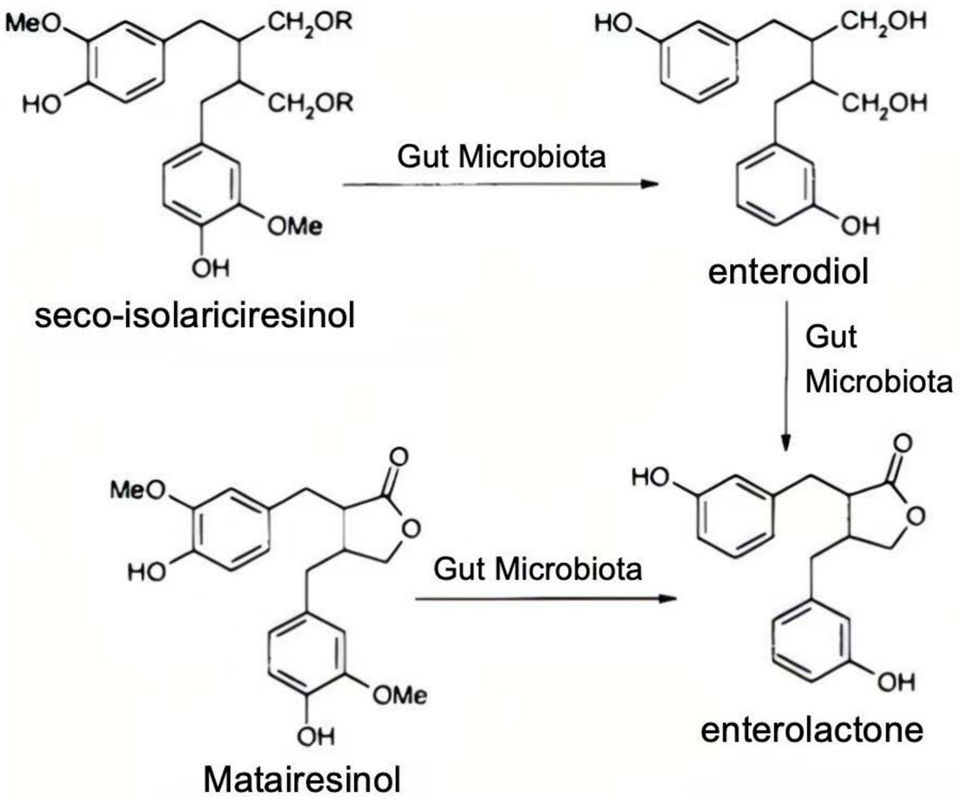

Figure 3 Absorption and metabolism of lignans.

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and Phase II conjugation reactions, transforming into water-soluble metabolites that are distributed via the bloodstream to target tissues.

Receptor Binding

Estrogen receptors (ER) are primarily classified into two subtypes: ERα and ERβ. ERα is predominantly expressed in tissues such as the uterus, mammary glands, and ovaries, which are highly responsive to estrogen. Conversely, ERβ is highly expressed in the brain, lungs, and prostate, serving as the main binding site in these tissues.[63]

Like endogenous estrogen, PEs interact with these receptors, exhibiting comparable distribution and functional mechanisms. Their metabolites exert biological effects mainly through two pathways (Figure 4).

Classical Estrogen Receptor Pathway

PEs competitively bind to estrogen receptors, activating classical genomic responses. The PE-receptor complex dimerizes and translocates into the nucleus, where it binds to estrogen response elements (EREs), thereby regulating the transcription of target genes.[64] This gene expression modulation mimics estrogen's physiological effects, contributing to the regulation of conditions such as osteoporosis and cardiovascular diseases in postmenopausal women.[65]

Non-Genomic Signaling Pathways

PE can also bind to membrane-associated estrogen receptors (mER), activating rapid non-genomic signaling cascades such as PI3K/Akt, ERK1/2, and cAMP/PKA pathways. These signals are typically completed within seconds to minutes and enable the swift regulation of cellular functions and metabolic processes.

Excretion and Enterohepatic Circulation

The metabolic fate of PE significantly influences its bioactivity and health benefits. In vivo, PE metabolites are primarily excreted via the kidneys, with approximately 60–70% in the form of glucuronide conjugates in urine, while the remainder

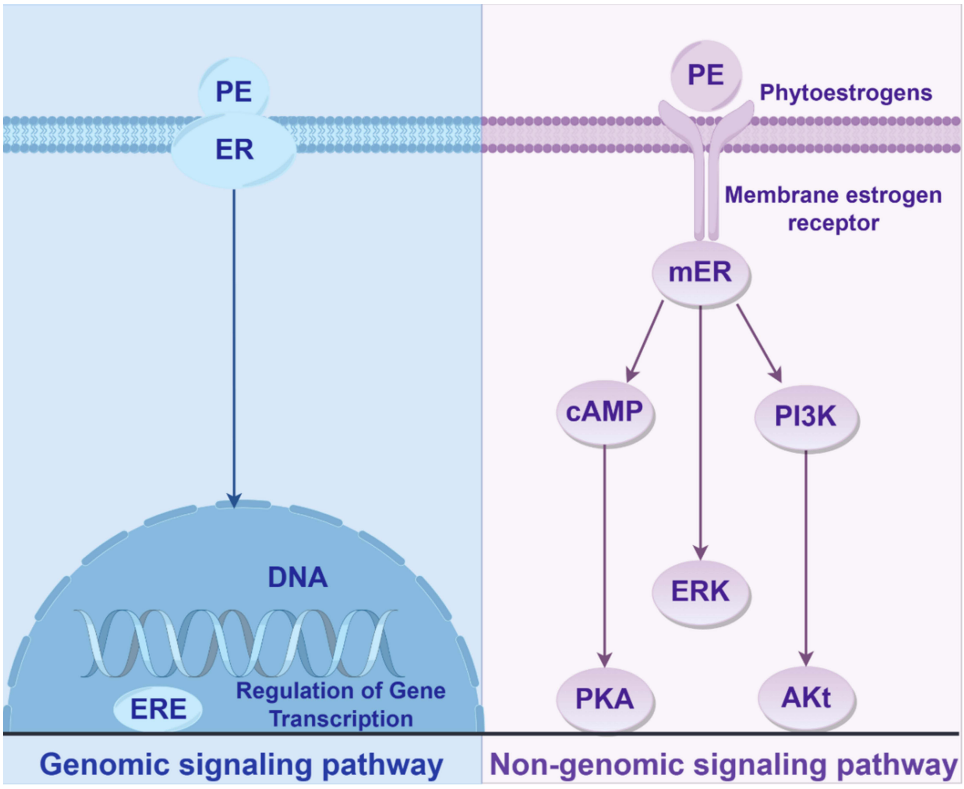

Figure 4 Genomic and non-genomic pathways of PEs binding to receptors.

is excreted into the intestine via bile. Gut microbiota's β-glucuronidases hydrolyze these conjugates, allowing free aglycones to be reabsorbed and participate in enterohepatic circulation, thereby markedly prolonging their half-life.[66] Studies indicate that the metabolism of soy isoflavones is relatively slow, with the half-life of soy aglycones reaching up to 8 hours.[67] This characteristic underpins the potential of soy isoflavones to modulate estrogen-related physiological functions and supports their prospective role in preventing and managing estrogen-associated diseases.

Effects of PEs on Exercise Capacity in Postmenopausal Women and Underlying Mechanisms

The decline in estrogen levels during menopause leads to reduced muscle protein synthesis, increased oxidative stress, and bone loss, collectively impairing physical performance and overall health. PE can mimic estrogen's effects, effectively improving exercise tolerance, muscle mass, and bone density, thereby enhancing physical capacity.[68]

The Effects of PEs on Postmenopausal Women's Muscle Protein Metabolism and Exercise Capacity

Estrogen deficiency impairs muscle protein synthesis, and PEs, due to their estrogen-like activity, are being explored as potential strategies to improve muscle metabolism. This section focuses on the regulatory mechanisms of PEs on muscle proteins in postmenopausal women and evaluates their practical benefits on exercise capacity.

Molecular Mechanisms of PEs in Regulating Muscle Protein Synthesis

Decreased estrogen levels are closely associated with reduced muscle protein synthesis. Although most mechanistic studies originate from animal models or cell experiments, they provide valuable insights into PEs' role in menopausal women. Research indicates that estrogen activates the mTOR signaling pathway, promoting ribosomal biogenesis and protein translation, thereby underpinning muscle growth and repair. Isoflavone-rich PE (such as dyewood flavonoids) can activate the Akt/mTOR pathway, upregulate the chaperone protein GRP78, and help maintain cellular protein homeostasis and optimize protein folding efficiency.[69,70] Flavonoid-based PE (such as apigenin and quercetin) modulate the MAPK/ERK and PI3K/AKT/mTOR pathways to promote myocyte differentiation and inhibit the NF-κB pathway, reducing TNF-α levels, thereby facilitating muscle regeneration and strength recovery, ultimately enhancing exercise capacity.[71–73]

Potential Effects of PEs in Suppressing Muscle Protein Degradation

The anti-proteolytic effects of PEs are crucial for maintaining muscle homeostasis. PEs reduce protein degradation by regulating proteasome activity. An RCT involving postmenopausal women demonstrated that daily intake of red clover extract (60 mg of isoflavones) combined with resistance training decreased the expression of proteolytic markers FOXO1/FOXO3a and increased protective heat shock proteins (HSP27). However, this intervention did not activate the mTOR pathway or improve muscle strength, suggesting that long-term intervention or combined training may be necessary for functional gains.[61] Animal studies show that genistein inhibits the expression of muscle atrophy-related genes Atrogin-1 and MuRF1 via ERβ pathways.[74,75] S-Equol, a metabolite of genistein, alleviates musculoskeletal pain, indicating its role in modulating protein metabolism through estrogen receptor pathways, thereby improving muscle health in postmenopausal women.[76]

Impact of Combined PEs and Exercise Interventions on Muscle Function: Controversies and Limitations

While estrogen supplementation can enhance strength training outcomes in menopausal women, and PEs such as soy isoflavones theoretically improve muscle function by mimicking estrogen pathways, clinical studies on postmenopausal women's exercise capacity yield conflicting results.

Some studies support a synergistic effect. A double-blind RCT showed that daily supplementation with 60 mg of soy isoflavones combined with 12 weeks of resistance training increased quadriceps cross-sectional area by 3.8% ($P<0.05$) and maximal isometric strength by 9.2%.[77] Another RCT involving women with sarcopenia confirmed that soy protein-

enriched milk combined with 16 weeks of resistance training significantly improved bench press and knee extension 1RM strength.[78]

Conversely, long-term intervention studies present differing conclusions. Fontvieille et al conducted a one-year trial indicating that although exercise training significantly improved lean body mass and physical function in overweight postmenopausal women, short-term metabolic improvements in muscle tissue were not further enhanced by PE supplementation, suggesting limited short-term metabolic and optimization effects during training.[79] Further, Choquette et al demonstrated that resistance plus aerobic training significantly increased maximal muscle strength, muscle mass, and relative strength (all $P<0.05$), whereas soy isoflavone supplementation alone showed no significant effects.[80]

In summary, exercise training remains the primary intervention for improving muscle function in postmenopausal women. While PEs may support muscle protein synthesis, current evidence for its clinical additive benefits is limited by heterogeneity in intervention protocols (such as duration, PE type, and dosage) and mechanistic understanding. Presently, PEs cannot be recommended as a universal strategy for muscle enhancement; systematic exercise interventions continue to be the preferred approach. Future research should focus on long-term studies to clarify the precise application and efficacy of PEs in this context.

The Potential Impact of PEs' Anti-Inflammatory and Antioxidant Properties on Exercise Capacity in Postmenopausal Women

Chronic low-grade inflammation and oxidative stress in postmenopausal women may significantly influence their exercise performance and overall physical adaptability. This section evaluates the evidence supporting PEs' anti-inflammatory and antioxidant mechanisms and explores their potential effects on exercise endurance and recovery in this population.

Preclinical Foundations of Anti-Inflammatory and Antioxidant Mechanisms and Their Limitations in Extrapolation

PEs exert synergistic anti-inflammatory and antioxidant effects through mechanisms such as inhibition of pro-inflammatory pathways, scavenging reactive oxygen species (ROS), and regulation of antioxidant enzymes. In vitro and animal studies indicate that lignan amides possess phenolic hydroxyl groups,[81] which may modulate gut microbiota to reduce post-exercise pro-inflammatory cytokine release, thereby alleviating systemic inflammation induced by high-intensity exercise.[82] Resveratrol activates the SirT1/PGC-1α pathway to promote mitochondrial biogenesis, extending exercise duration by enhancing muscular endurance, and improves energy utilization during high-intensity activity via the AMPK pathway.[83–85] Flavonoids like flavonoids inhibit ROS-mediated macrophage pyroptosis,[86] while quercetin may protect the PI3K/Akt/FOXO3 pathway from exercise-induced cardiac stress, and estrogenic compounds such as equol can modulate activities of antioxidant enzymes like SOD and GPx. These findings suggest that PE could mitigate exercise-induced oxidative damage and inflammatory responses, improve energy metabolism, and theoretically enhance endurance and recovery. However, results from animal models cannot be directly extrapolated to human postmenopausal women.

Human Evidence on the Effects of PEs on Exercise Capacity and Recovery in Postmenopausal Women

Given the well-documented anti-inflammatory properties of PEs and considering the prevalent chronic inflammation and oxidative stress in menopausal women that may significantly impair their physical performance, exploring the synergistic effects of PEs supplementation combined with regular exercise holds substantial clinical relevance. Multiple clinical studies provide compelling evidence supporting this approach.

A recent 12-week RCT demonstrated that combined intervention with soybean and hops extracts—rich in isoflavones—significantly alleviated symptoms such as fatigue, arthritis, and myalgia in menopausal women.[87] Although this study did not directly assess exercise performance, the amelioration of these symptoms likely contributes to reduced exercise-induced muscle discomfort and inflammatory responses, thereby facilitating faster muscle recovery and potentially enhancing exercise tolerance.

Further, research by Llaneza et al offers more direct evidence.[88] Over a 24-month intervention, participants receiving soy isoflavone supplementation alongside exercise and a Mediterranean diet exhibited not only lower BMI and adiposity but also a marked reduction in tumor necrosis factor-alpha (TNF-α) levels. These findings suggest that PEs may indirectly improve exercise endurance and recovery by improving body composition and attenuating systemic inflammation.

Regarding skeletal muscle adaptability, a study investigating the effects of Shatavari—a herbal supplement containing PEs—found that this phytotherapeutic agent significantly upregulated pathways involved in metabolic regulation and cellular repair.[89] This intervention appeared to influence postmenopausal women's body composition and muscle function markers, indicating that Shatavari's anti-inflammatory and antioxidant properties may modulate muscle function and mitigate post-exercise muscle inflammation. Nonetheless, the specific impact of Shatavari on exercise-induced inflammatory responses warrants further validation through controlled exercise interventions.

Conversely, the findings of Riesco et al are comparatively conservative.[90] Their study indicated that soy isoflavone supplementation did not produce a more significant reduction in serum C-reactive protein (CRP) and leptin levels in postmenopausal women than exercise alone, suggesting that physical activity itself exerts substantial anti-inflammatory effects. However, the authors propose that PEs may exert indirect benefits by modulating other adipokines involved in recovery processes.

In summary, current clinical evidence suggests that specific PEs supplementation may influence exercise capacity in menopausal women through multiple mechanisms, including improvements in body composition, reductions in inflammatory biomarkers such as TNF-α, and attenuation of post-exercise inflammatory responses. These effects may collectively support the maintenance of exercise endurance and optimize recovery, although the magnitude and nature of these benefits likely depend on the type of PEs and intervention protocols employed. Future research should aim to more directly evaluate the immediate and long-term impacts of PEs on exercise performance.

The Impact of PEs on Cardiovascular and Metabolic Health and Exercise Capacity in Postmenopausal Women

The decline in estrogen levels following menopause is closely associated with increased cardiovascular disease risk and disturbances in glucose and lipid metabolism. PEs may indirectly influence exercise capacity by improving these metabolic parameters. This section focuses on the underlying regulatory mechanisms and evidence from population studies to explore the potential effects of PEs on cardiovascular metabolic health and physical performance in postmenopausal women.

Potential Regulatory Mechanisms of PEs on Cardiovascular and Metabolic Health

Preclinical studies suggest that PEs may modulate metabolic functions through multiple pathways, providing a biological basis for their potential effects. In glucose metabolism, lignans and isoflavones can activate estrogen receptors or AMP-activated protein kinase (AMPK) pathways to promote glucose uptake in skeletal muscle and adipose tissue,[91,92] thereby enhancing insulin sensitivity and regulating hepatic enzymes critical for glucose metabolism, such as glucokinase (GK) and glucose-6-phosphatase (G6Pase).[4,93] Regarding energy metabolism, PEs may influence mitochondrial function via ERs or G protein-coupled estrogen receptor (GPER) signaling,[94,95] with ERα playing a key role in maintaining exercise endurance and supporting sustained physical performance.[96,97] In lipid metabolism, isoflavones can regulate the expression of lipogenic genes in the liver and adipose tissue, such as SREBP-1c, FASN, and SCD1, thereby improving lipid profiles.[98,99] Coumarin derivatives of PEs may also affect fat distribution by activating brown adipose tissue or modulating gut microbiota.[100–102] Additionally, some PEs promote endothelial nitric oxide (NO) release, improving endothelium-dependent vasodilation, which is crucial for maintaining effective blood flow during exercise.[103]

Effects of PEs on Postmenopausal Women: Cardiovascular Metabolic Health and Exercise Capacity

From an exercise physiology perspective, the synergistic effects of PEs on exercise-induced metabolic improvements warrant further investigation. Most current studies assess the potential impact of PEs on exercise capacity through

changes in metabolic biomarkers. Multiple studies indicate that PEs may provide a physiological basis for enhanced exercise performance by improving glucose and lipid metabolism and cardiovascular function.

In glucose metabolism, a meta-analysis focusing on non-Asian postmenopausal women reported that soy isoflavone supplementation was associated with significant weight loss, reductions in fasting blood glucose, and decreased insulin levels.[104] While these metabolic improvements could theoretically enhance exercise efficiency, direct assessments of exercise performance were not conducted. Notably, an intervention study on insulin-resistant postmenopausal women found that, on a basis of 6–24 months of Mediterranean diet and walking exercise, an additional daily intake of 40 mg soy isoflavones significantly lowered HOMA-IR indices ($P<0.05$), with effects persisting during follow-up, suggesting that PEs may augment exercise-related improvements in insulin sensitivity, offering additional metabolic benefits.[105]

Regarding lipid metabolism, optimizing lipid profiles may represent another key mechanism. Llaneza et al observed that while diet control (1200 kcal) and exercise improved adipokine levels (leptin and adiponectin) in obese postmenopausal women, only combined supplementation with 80 mg/day soy isoflavones significantly increased serum adiponectin levels.[106] This "exercise-phytoestrogen" synergy may improve metabolic environments through multiple pathways, serving as a critical regulatory mechanism for cardiovascular health in menopausal women and supporting exercise capacity.

In terms of cardiovascular function, physical activity and phytoestrogen supplementation appear to be potential strategies for preventing cardiovascular disease in postmenopausal women; however, current findings are somewhat inconsistent. Dechichi et al reported that in normotensive postmenopausal women, 10 weeks of exercise training significantly reduced blood pressure, but additional supplementation with 100 mg/day soy isoflavones did not produce further effects.[107] Conversely, a meta-analysis indicated that daily intake of ≥25 g soy protein containing ≥100 mg/d isoflavones was associated with significant blood pressure reductions.[108] These discrepancies may reflect dose-dependent effects of PEs and population-specific responses, as well as the inherent capacity of exercise training to modulate blood pressure.

In summary, existing evidence suggests that PEs may indirectly support exercise capacity by improving metabolic parameters. However, most studies lack direct assessments of exercise performance metrics such as VO2max or endurance time, limiting definitive conclusions regarding their practical efficacy. Future research should systematically investigate the direct effects of PEs on exercise capacity.

The Interactive Effects of PEs on Bone Health Preservation and Motor Function in Perimenopausal Women

Bone health constitutes a central challenge in maintaining health post-menopause. The decline in estrogen levels following menopause accelerates bone loss, thereby increasing fracture risk and impairing key components of motor function. PEs may exert osteoprotective effects through mechanisms such as regulation of osteocyte activity, modulation of metabolic signaling pathways, and maintenance of calcium homeostasis, thereby indirectly supporting motor function.

Molecular and Cellular Mechanisms of PEs in Bone Protection

PEs potentially influence bone metabolism via multiple pathways, primarily evidenced by in vitro studies and ovariectomized animal models, which suggest potential routes for PEs in alleviating orthopedic diseases and improving motor function in postmenopausal women. For instance, equol activates ERβ to regulate the OPG/RANKL balance, promoting osteogenesis;[109] isobavachalcone enhances osteogenic differentiation of bone marrow stromal cells (BMSCs);[110] and phellodendrine reduce osteoarthritis progression by inhibiting ERK/NFATc1 signaling.[111] Additionally, PEs can modulate signaling pathways such as Wnt/β-catenin to promote bone formation and activate the Keap1/Nrf2/ARE antioxidant pathway to protect osteocytes.[112,113] The combined supplementation of isoflavones and calcium may also maintain bone mineral density by regulating vitamin D activity, thereby improving calcium homeostasis and metabolic processes.[114]

Population Evidence: The Impact of PEs on Postmenopausal Bone Health and Its Translation to Motor Function

Building upon the aforementioned potential mechanisms, numerous clinical studies have explored the effects of PEs on bone health in postmenopausal women and their functional implications. Notably, soy isoflavones—known for their

specific effects on bone—may influence bone density indirectly by affecting bone metabolic hormones such as parathyroid hormone.[115]

Meta-analyses indicate that soy isoflavones significantly inhibit bone resorption and stimulate bone formation,[116] although effects vary markedly depending on dosage and population. An Italian RCT demonstrated that a daily dose of 54 mg, through bidirectional regulation of bone metabolism, improved lumbar spine and hip Bone Mineral Density (BMD) in early postmenopausal women comparably to HRT, without inducing endometrial hyperplasia.[117] Conversely, similar doses in American populations showed limited efficacy in preventing hip osteopenia.[118–120]

In a North American study, Phani et al observed that consuming 90 g of soy protein containing isoflavones prevented significant femoral trochanter bone loss.[121] An Asian study by Chen et al found that an 80 mg/d dose effectively increased bone mineral content (BMC) at the hip, especially at the greater trochanter, in women with low bone mass.[122] However, a Taiwanese RCT indicated that a higher dose of 300 mg/d yielded no significant benefits.[123] A European study administering 110 mg/d of soy isoflavones in fortified foods for one year failed to slow lumbar or overall skeletal BMD decline or improve bone turnover markers.[124] The heterogeneity observed across studies may be attributable to genetic backgrounds, baseline dietary intake, and differences in formulations (pure isoflavones versus soy protein).

The synergistic effects of exercise interventions combined with PEs supplementation exhibit complex dose-response relationships. A two-year RCT revealed that resistance combined with aerobic exercise alone, or with 165 mg/d of isoflavones, provided comparable protection of hip BMD; however, their combination unexpectedly accelerated bone loss, suggesting potential dose-dependent negative interactions.[125] The most direct clinical evidence comes from a study on flaxseed lignans, which showed that a daily 50 mg dose over six months significantly increased six-minute walk distance and knee extensor strength, thereby confirming PE's role in modulating bone metabolism and translating into tangible improvements in functional mobility and quality of life.[126]

Metabolite research indicates that equol, a gut microbiota-derived metabolite of soy isoflavones, exhibits notable osteoprotective effects in preclinical studies.[127] Clinical investigations further demonstrate that combined interventions with equol and resveratrol significantly improve bone turnover markers such as osteocalcin;[128] however, long-term effects on BMD and motor function in postmenopausal women require further clinical validation.

In summary, PEs may indirectly enhance motor capabilities—such as balance, endurance, and muscle strength—by improving bone health, with some effects mediated through pain reduction and activity limitation alleviation. Future research should focus on elucidating how PE interventions translate into actual improvements in motor function and quality of life.

Regulation of Neurotransmitter-Motor Performance Axis by Physical Exercise: Mechanisms and Translational Implications for Perimenopausal Women

Physical exercise may influence neurofunctional and motor performance in perimenopausal women through modulation of neurotransmitter systems. Key neurotransmitters such as serotonin and dopamine are integral to motor control and coordination, and their homeostasis may be disrupted by endocrine changes during menopause, leading to complex effects on motor capabilities.

Molecular Evidence for Neurotransmitter Regulation

Preclinical studies indicate that flavonoids like quercetin possess neuroprotective properties and the capacity to modulate neurotransmitter activity. Animal experiments demonstrate that quercetin can regulate histone acetylation, thereby reducing endoplasmic reticulum stress protein expression in the hypothalamus and improving mitochondrial function.[129] Additionally, research shows that quercetin (40 mg/kg) can modulate nitric oxide levels, alleviating depression-like behaviors induced by social isolation, suggesting promising therapeutic potential for stress-related emotional disturbances.[130]

Impact of Physical Exercise on Neurocognitive-Motor Integration in Perimenopausal Women

Clinical investigations suggest that specific PEs interventions may indirectly enhance motor performance in perimenopausal women by improving neurocognitive functions. A 40-week randomized controlled trial by Nakamura et al

demonstrated that daily supplementation with 110 mg of quercetin glycosides significantly improved cognitive response speed in elderly women, including postmenopausal individuals.[131] Given the close association between response speed, fall risk, and motor task performance,[132] this finding implies that quercetin glycosides may enhance neuromuscular coordination, thereby improving motor safety.

Research on resveratrol also holds clinical relevance in the context of neurocognitive health among menopausal women. Two RCTs confirmed its efficacy in improving cerebrovascular reactivity and cognitive function during movement in postmenopausal women,[133,134] supporting complex motor control and alleviating osteoarthritic pain.[135] These combined effects may enhance exercise tolerance and adherence, establishing a foundation for maintaining or improving long-term motor capacity. Furthermore, RCTs from Asian and North American populations indicate that soy isoflavones can improve visual memory in postmenopausal women, although they do not directly influence baseline motor abilities.[136,137] Nonetheless, such cognitive benefits may promote more active engagement in physical activity, with broader implications for cognitive health and participation in diverse sports activities.

Collectively, these findings suggest that PEs may support motor performance in perimenopausal women through multiple neurocognitive pathways. However, the precise mechanisms underlying these effects warrant further detailed investigation.

Conclusions and Limitations

The impact of physical exercise on postmenopausal women's physical capacity is modulated by multiple factors, including the type, dosage, source (dietary versus supplemental), and individual metabolic differences, underscoring the importance of personalized application. Certain specific types of PEs demonstrate potential in supporting postmenopausal women's physical performance through multiple pathways, potentially exerting beneficial effects on relevant physiological markers and adaptive processes. Current evidence indicates that: 1) PEs can regulate muscle protein metabolism, serving as a personalized adjunct to enhance physical performance, although the central role of structured exercise training remains irreplaceable; 2) their anti-inflammatory and antioxidant properties may indirectly promote improvements in physical capacity by ameliorating postmenopausal inflammatory states and oxidative stress; 3) PEs hold potential regulatory value for cardiovascular and metabolic health in this population; 4) their effects on bone metabolism appear to be influenced by multifactorial interactions, including dosage, demographic characteristics, and intervention modalities; 5) they may indirectly support neuromuscular and cognitive functions through modulation of neurotransmitter systems. These findings suggest potential non-hormonal strategies to address declines in physical capacity associated with estrogen deficiency.

Despite the promising insights, the field faces significant challenges, notably the scarcity of high-quality, large sample RCTs directly assessing the effects of PEs on specific physical performance endpoints in postmenopausal women, such as VO2max, muscle strength, and fatigue recovery. Most existing evidence derives from studies targeting general health indicators, observational research, or animal models, rather than dedicated assessments of exercise performance metrics. Furthermore, the mechanisms underlying PEs' effects on musculoskeletal and neural tissues, as well as their interactions with exercise interventions, require further elucidation. Variability in bioavailability and metabolic responses among individuals further complicates research efforts.

Future investigations should prioritize large-scale, long-duration RCTs to systematically evaluate the effects of PEs on specific physical performance parameters, including muscle strength, endurance, balance, and post-exercise recovery. Additionally, research should aim to determine optimal dosing, timing, and long-term safety profiles of different PEs modalities, as well as to develop personalized intervention strategies based on individual characteristics. Such studies are essential for scientifically assessing the role of PEs in healthy aging and for optimizing physical performance outcomes in postmenopausal women.

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Disclosure

The author(s) report no conflicts of interest in this work.

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