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Epimedium and Its Flavonoids as Multi-Target Anti-Aging Agents: A Systematic Review of Preclinical and Clinical Evidence

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ABSTRACT

Aging arises from numerous biological influences, including genetic factors, oxidative stress, metabolic imbalance, immune dysregulation, and alterations in sex hormones. This review summarizes how Epimedium may slow aging by examining six major dimensions: gene-related actions, antioxidant capacity, metabolic effects, immune modulation, hormone-related regulation, and clinical performance.Through an extensive survey of existing research, the goal was to identify the possible pharmacological pathways through which Epimedium contributes to delayed aging.Published evidence concerning Epimedium's uses across multiple bodily systems and possible mechanistic bases was assessed using a systematic, integrative approach. The review focuses on gene-associated processes, antioxidation, metabolic regulation, immune activity, hormonal effects, as well as clinical benefit and safety considerations.Flavonoids—including Epimedins A, B, C, and icariin—appear to represent the principal anti-aging agents in Epimedium. Its potential to delay aging seems linked to gene modulation, antioxidant activity, metabolic adjustment, immune responses, and endocrine-related regulation. No serious adverse events have been documented.Epimedium exhibits promising anti-aging properties and is widely employed in China for conditions associated with aging; nonetheless, broader and more rigorous studies are still required.

Keywords: Epimedium, Aging, Antioxidant, Mechanism, Metabolism

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Introduction

Aging is a multifaceted biological progression that heightens vulnerability to health problems [1] and represents a major global challenge. It substantially affects quality of life and shapes modern health policy. Traditional Chinese medicines (TCMs), as core elements of complementary and alternative therapeutics, may offer valuable strategies for mitigating age-related decline.

From the standpoint of TCM, Epimedium (family Berberidaceae) is believed to restore vitality and has been included for centuries in classical prescriptions based on its role in "kidney nourishment and Yang enhancement" [2, 3]. Contemporary research indicates that Epimedium exhibits numerous pharmacological activities, such as anti-aging effects, protection against bone loss, enhancement of immune function, antidepressant properties, cardioprotective actions, improvement of erectile function, and potential antitumor benefits [4–6]. It is also commonly combined with other herbal agents to manage age-associated disorders, including cardiovascular disease, sexual dysfunction, immune weakness, and menstrual irregularity [7–9]. Although modern biomedical understanding does not equate aging with sexual function, TCM theory connects aging with diminished kidney qi, for which sexual decline is considered a hallmark.

Known by various names—including Barrenwort, Rowdy Lamb Herb, Horny Goat Weed, and in Chinese as Yin Yang Huo, Yang He Ye, or Xian Ling Pi **(Figure 1)**—Epimedium is a traditional herb or tea component. It comprises a genus of perennial woodland plants typically found beneath forest canopies, in thickets, or on

mountain slopes ranging from 650 to 3000 m in altitude. As the largest herbaceous group within Berberidaceae, the genus includes approximately 62 species. Distribution is discontinuous across the Old World, spanning the Mediterranean, western Asia, and eastern Asia. Five species occur in Algeria and the Caucasus, six in Japan, Korea, northeastern China, and the Russian Far East, and roughly 51 in central and southeastern China. Thus, China serves as the primary center of diversity and distribution for this genus [10].

Medicinal Epimedium is produced from the dried aerial sections of Epimedium wushanense T.S. Ying, E. sagittatum Maxim, E. brevicornum Maxim, E. koreanum Nakai, and E. pubescens Maxim, which are cultivated in provinces such as Sichuan, Shanxi, Liaoning, and Gansu [11]. Processing methods include stir-frying with suet, wine treatment, fire moxibustion, and the use of salt or butter, with suet stir-frying being the most widely applied technique **(Figure 2)** [12].

The plant contains numerous flavonoids, collectively called Epimedium flavonoids (EFs), with icariin (ICA; molecular formula C33H40O15) recognized as a primary active molecule [13]. Other constituents include prenylated flavonoids, polysaccharides, alkaloids, phytosterols, terpenoids, chlorogenic acid, and several additional bioactive substances [14, 15]. Across 17 species, over 141 distinct flavonoids have been described—such as chalcones, flavones, flavonols, flavonol glycosides, and flavanones [16]. Additionally, 31 lignans and their glycosides, 12 ionones and derivatives, and six phenethyl alcohol glycosides have been identified. Compounds including xanthones, aldehydes, organic acids, and alkaloids are also present. Epimedins A, B, C, and ICA together account for roughly 52% or more of total flavonoids and are considered the major functional ingredients **(Figure 3)** [16].

Figure 1. Illustration of Epimedium derived from its dried above-ground portions.

Figure 2. Yangheye becomes an ingredient in traditional prescriptions after being processed by stir-frying with suet.

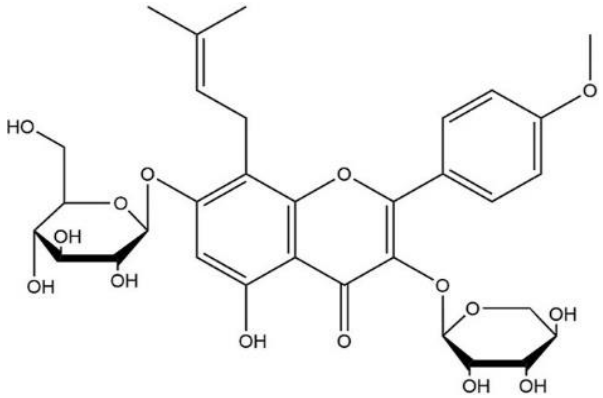

Figure 3. Epimedium contains primarily flavonoids and alkaloids, with Epimedium flavonoids (EF) as the dominant fraction; icariin (ICA, molecular formula C33H40O15) is the principal active monomer.

Potential mechanism of Epimedium in slow-aging

Gene regulation

Aging-related genes

Recent findings indicate that Epimedium may mitigate aging by altering the expression profiles of genes associated with senescence. Huang [17] observed an age-dependent expression pattern across 199 genes, most of which were shifted toward youthful levels after Epimedium administration. In a neural network analysis, Epimedium adjusted the transcriptome of 24-month-old rats to resemble that of 8–13-month-old animals. Out of 1885 detected metabolic peaks, 17 metabolites exhibited age-sensitive variation, and Epimedium treatment restored their levels to those typical of approximately 18-month-old rats. Additionally, p16 mRNA expression rises with human aging, and Epimedium may suppress p16 activity to limit cellular senescence [18]. Lowering p16 expression helps maintain DNA repair functions and is linked to lifespan extension. Collectively, these studies imply that Epimedium may counteract aging through modulation of senescence-related genes and their pathways.

Longevity-related genes

Regulation of genes related to lifespan appears to play a key role in delaying aging and reducing disease burden [19]. Liu [20] demonstrated that EF moderately enhanced nuclear factor kappa-B (NF-κB) signaling through the IKK/IκB/Rel/NF-κB cascade by influencing IκBε and IκBα in elderly rats. Sixty Sprague–Dawley rats were separated into six age-defined groups: 3-day (d), 4-month (m), 10 m, 18 m, 27 m, and 27 m + EF. NF-κB-associated kinase mRNA levels declined progressively with age in splenic lymphocytes, reaching a maximum at 3 days and minimum at 18–27 months. EF intervention elevated these levels in aged rats to those observed at roughly 10–18 months. These outcomes provide evidence that EF helps delay aging.

Chen [21] reported that lymphocyte apoptosis rates differed significantly between older and young rats, with an EF-treated group showing improvement relative to older controls ($P < 0.01$). Compared with the young rats, the older group showed 116 genes upregulated and 215 downregulated. In comparison with aged controls, EF-treated animals had 447 upregulated and 456 downregulated genes, involving pathways related to apoptosis and cell proliferation. EF appears to counterbalance detrimental gene-expression shifts—reversing excess apoptotic signaling and enhancing proliferative capacity—to restore immune stability during aging. Overall, Epimedium and its constituents modulate lifespan-related genes and promote gene-expression patterns supportive of healthy aging.

Anti-DNA damage

Icariin (ICA) represents the major bioactive compound in Epimedium. Numerous studies have shown ICA's protective antioxidant effects against β-amyloid toxicity, DNA injury, and oxidative stress in vascular endothelial cells [22]. Relative protein levels of NQO1, HO-1, and Nrf2 in the testes were significantly elevated by ICA compared with an aging model group, whereas γ-H2AX, p-p53, and p21 levels were reduced. ICA therefore alleviates DNA damage in testicular germ cells of naturally aging rats, likely via activation of the Nrf2/HO-1 pathway [23]. Zhao's work revealed that total flavone of Epimedium (TFE) decreased γH2AX expression in spermatogonia and primary spermatocytes, reduced γH2AX foci, and concurrently lowered 8-OHdG levels [24].

TFE also suppressed expression of p-P53/p21 and chk1/chk2, indicating that a p53-dependent pathway contributes to its effects in reducing oxidative DNA injury in aging rat testes. Chen further showed that TFE significantly counteracted mitomycin C (MMC)–induced DNA damage in mouse bone marrow cells, demonstrated by reduced comet cell proportion and shortened tail length, with a clear dose–response relationship [25]. These findings confirm that TFE offers strong protection against DNA damage in bone marrow lymphocytes exposed to MMC.

Antioxidant

Anti-free radical

In the 1950s, Harman introduced the free-radical hypothesis of aging [26], proposing that age-related decline results from cumulative oxidative injury to macromolecules such as lipids, DNA, and proteins caused by reactive oxygen and nitrogen species from internal and external sources [27]. Excessive free-radical buildup damages cells, tissues, and organs, ultimately driving aging. Epimedium has multiple modes of action against aging, including effects on endocrine function, immune balance, metabolism, and organ performance. EFs have been shown to lower oxygen levels in isolated hepatic tissue cultures. Investigators have reported that Epimedium neutralizes free radicals and diminishes their reactivity. Zhao [28] demonstrated strong antioxidant potential of Epimedium-derived phenolic compounds. In aged mice, Epimedium substantially increased activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) in erythrocytes while markedly decreasing serum and hepatic lipid peroxide (LPO) levels and reducing cardiac lipofuscin (LF) content. These outcomes suggest that EF may serve as an anti-aging factor by enhancing SOD and GSH-Px and limiting LPO and LF accumulation [28]. Zhang [29] confirmed that ICA is a key contributor to the plant's antioxidant capacity, and Liu [30] verified that ICA acts as a potent and efficient antioxidant.

Against D-galactose–induced aging

Subcutaneous D-galactose (D-gal) administration can rapidly induce senescence in laboratory animals, mimicking natural aging mechanisms [31]. To explore whether Epimedium counteracts D-gal–evoked senescence in H9c2 cells, Li [32] used 50 mmol/L D-gal to trigger aging in these cells. Epimedium treatment reduced β-galactosidase-positive cell counts, lowered malonaldehyde (MDA) concentrations, decreased ROS fluorescence intensity, enhanced SOD activity, and improved chromatin conditions. ICA, one of Epimedium's major flavonoid components, was further examined in D-gal–treated rats with a focus on tyrosine kinase TrkB (tropomyosin receptor kinase B). Using the Morris water maze, investigators observed that chronic D-gal injections (500 mg/kg/d for four months) produced memory impairment. Structural disruption of hippocampal neurons, diminished brain-derived neurotrophic factor (BDNF), and reduced TrkB expression were also reported. Daily oral ICA (60 mg/kg/d), administered 1 h after each D-gal subcutaneous dose for the same four-month duration, significantly mitigated the behavioral and neuronal deficits—shorter escape latency, decreased search distance, and recovery of neuronal morphology. These findings highlight that prolonged D-gal exposure leads to cognitive decline, while ICA protects neural tissue and ameliorates memory disturbances [33] in D-gal–aged mice [29, 34].

The regulation of metabolism

Cellular metabolism

Cheong [34] demonstrated that EF promotes the proliferation and migration of adrenocortical stem cells in corticosterone-treated rats, a commonly used model of Shen-yang deficiency. The study showed that EF increased the expression of growth hormone (GH), insulin-like growth factor-binding protein (IGFBP), and growth hormone-releasing hormone (GHRH) via gene-chip analysis, suggesting that EF enhances endocrine hormone secretion. Gao [35] reported that EF protected H9c2 cells against D-gal–mediated senescence by boosting antioxidant capacity and lowering apoptosis. Homocysteine was shown to markedly elevate cellular senescence both in vivo and in vitro, while Xiao [36] found that ICA delayed homocysteine-induced endothelial aging through activation of the PI3K/Akt-eNOS pathway.

Together, these findings indicate that EF and its derivatives may counter glucocorticoid-mediated suppression of the hypothalamus–pituitary–adrenal (HPA) axis and delay stem-cell aging, forming a potential cytological mechanism for slow-aging effects. In TCM theory, age-related disorders can be alleviated by stimulating endogenous stem cells, elevating hormone and cytokine production, and shifting the organism toward a more active physiological state. Harnessing endogenous stem-cell activation provides a novel therapeutic perspective for degenerative disease management.

Osteoporosis—defined by reduced bone mineral density and heightened fracture risk—is prevalent in older adults, particularly in postmenopausal women [37, 38]. In TCM practice, herbal therapies are widely used for osteoporosis prevention and management, with Epimedium being one of the primary choices [39]. Within TCM concepts, Epimedium supports skeletal health by strengthening kidney function. Earlier findings indicate that Epimedium improves bone turnover, elevates bone mineral content, and helps restore trabecular bone integrity, structure, and biomechanical strength [40, 41].

A PubMed search using terms such as osteoporosis, postmenopausal osteoporosis, Epimedium, barrenwort, Bishop's hat, fairy wings, horny goat weed, and Yin Yang Huo identified six preclinical studies assessing its anti-osteoporotic activity. One experiment showed that ICA, a prenylated flavonol glycoside, enhanced peak bone mass in young rats and promoted osteoblast maturation and mineralization in rat calvarial cells [42]. Another reported that icaritin stimulated osteogenesis while suppressing adipogenic differentiation in marrow mesenchymal stem cells [43]. Overall, preclinical evidence suggests that Epimedium supports bone mineral density (BMD) and increases bone-formation rates.

Lipid metabolism

Metabolomic exploration of Epimedium and its bioactive compounds indicates involvement in multiple pathways, including TOR, AMPK, SIR-2, and IIS—many of which overlap with dietary-restriction mechanisms. Epimedium reduced total cholesterol (TC) and triglycerides (TG) in hyperlipidemic rat models. Hu [44] assigned 70 rats into five groups and treated them daily with normal saline, simvastatin, or ICA (30 mg/kg/d or 60 mg/kg/d) for 4 weeks. Blood lipid indices, SOD, and MDA levels were measured. Hyperlipidemic rats exhibited elevated TC, TG, LDL-C, and MDA, along with decreased HDL-C and SOD. ICA reversed many of these abnormalities, likely through anti-inflammatory and antioxidant mechanisms, and has been recognized for lipid-lowering effects in various cardiovascular conditions.

Liquid chromatography–mass spectrometry (LC/MS) metabolomics was applied by Yan [45] to characterize rat aging patterns across groups at 4, 10, 18, and 24 months, including TFE-treated rats. Age-related shifts were identified in metabolites such as saturated/unsaturated fatty acids and amino acids. Administration of TFE restored most of these markers toward youthful profiles. These results suggest that lipid metabolic alterations and free-radical accumulation are hallmarks of aging, and that TFE may exert slow-aging effects through lipid-regulating and antioxidant properties.

To further assess Epimedium's slow-aging potential, Wu [46] analyzed urinary metabolites from 4-, 10-, 18-, and 24-month-old rats treated with TFE. Metabonomic results identified 26 resonances strongly associated with aging. After TFE intervention, many of these markers shifted toward patterns characteristic of younger animals. These metabolites included creatinine derivatives, aliphatic amines, and key intermediates or end products of energy metabolism. The findings suggest that TFE can delay aging by improving pyruvate metabolism and oxidative phosphorylation. Collectively, these studies support Epimedium as a promising candidate for slow-aging interventions.

Bone metabolism

A search of PubMed in English yielded four clinical trials investigating Epimedium's effect on osteoporosis. One 24-month, randomized, double-blind, placebo-controlled trial in Hong Kong, China, examined Epimedium-derived phytoestrogen flavonoids (EPFs) on BMD in postmenopausal women [8]. In total, 100 healthy women in late postmenopause were randomly assigned to the EPF group (n = 50; daily intake: 60 mg ICA, 15 mg daidzein, 3 mg genistein) or a placebo group (n = 50). EPF treatment preserved BMD at 12 and 24 months, whereas the control group experienced declines, with significant differences between groups [8]. No changes were observed in serum estradiol or endometrial thickness in either group [8]. Another trial assessed medicinal cake-separated moxibustion for elderly osteoporosis [39], where Epimedium, the main component of the topical medicinal cake, improved clinical symptoms, increased BMD, and reduced serum β-type I collagen carboxy-terminal peptide. A separate 5-year multicenter follow-up in Mainland China included 194 postmenopausal women, comparing kidney-tonifying herbal Fufang combined with phytoestrogenic Epimedium (10 g/day, twice daily, n = 101) against placebo (n = 93) [47]. All participants received calcium and vitamin supplements [47]. After 5 years, the herbal Fufang group showed significant BMD gains from baseline, while the placebo group had BMD loss ($p < 0.05$). Fracture risk was lower in the Fufang group, with a relative risk of 0.57 (95% CI, 0.43–0.70, $p < 0.05$) [47].

Modulation of the immune system

T and B lymphocytes

Cellular immunity declines with age, a process termed immune senescence, partly driven by thymic involution and chronic low-grade inflammation in the elderly, which may accelerate cognitive decline [48]. T and B lymphocytes are key contributors to immune senescence [17, 49, 50]. Rhew [51] reported that ICA can function as an immune adjuvant. In mice, ICA at 10 mg/kg/day suppressed immune activity and extended allograft skin survival [52]. Wang [53] demonstrated that Epimedium enhanced CD3+, CD4+, CD8+, CD19+, and NK cell counts in the spleen ($P < 0.05$) and increased bone marrow cells in hemodialysis patients. In delayed-type hypersensitivity mouse models, Epimedium increased CD4+ T-lymphocyte levels. Epimedium also restores T-cell immune homeostasis by reducing excessive splenic lymphocyte apoptosis and activating the Rel/NF-kappaB/I B/IKK pathway, ultimately upregulating NF-kappaB via modulation of I Bepsilon and I Balpha.

Immuno-homeostasis

Age-associated immune imbalance involves abnormal expression of genes that control apoptosis. Epimedium can counteract these dysregulations by modulating pro- and anti-apoptotic genes and genes that enhance or inhibit proliferation, thereby restoring immune homeostasis in older individuals [21].

Neuroendocrine-immune network

In the study by Cai [54], the anti-aging effects of ICA and its three derivatives—Icariside I, Icariside II, and Icaritin—were evaluated in C. elegans. Results showed that ICA and Icariside II extended the lifespan of adult nematodes. Moreover, in rodent experiments, Icariside II delayed aging-related traits, indicating its potential to promote healthy aging. The authors suggested that Icariside II might influence longevity in C. elegans via the IIS signaling pathway. Additional investigations examined the impact of ICA on hippocampal BDNF and TrkB mRNA levels in naturally aged rats. BDNF, a member of the neurotrophin family, supports neuronal growth and survival and is linked to cognitive function [33]. Findings indicated that aging and stress conditions affected BDNF and TrkB mRNA regulation, potentially influencing hippocampal damage and repair mechanisms. ICA treatment improved neuronal organization and reduced degeneration. Compared with controls, ICA elevated BDNF and TrkB mRNA expression in the hippocampus, suggesting its anti-aging effects may be mediated through these neurotrophic pathways. In another study, Zhang [55] demonstrated that ICA enhanced mitochondrial function, suppressed beta-amyloid (Aβ) production, and increased neurotrophic factor expression in sodium azide-induced rat brain models. Overall, Epimedium appears to extend adult lifespan through the IIS pathway, upregulate hippocampal BDNF and TrkB mRNA during aging, and stimulate neurotrophic factor expression in the brain.

Inflammation-aging

Aging is often accompanied by persistent, low-level inflammation, a phenomenon termed inflammaging [35, 36, 44]. Epimedium exhibits broad anti-inflammatory, antibacterial, and antiviral activities. Ti's experiment indicated that among ten tested compounds, compound 6 exhibited the strongest anti-inflammatory activity in vitro, with a maximal inhibition rate of 79% [45]. In antibacterial assays, diphylloside A, icarisoside A, and desmethylanhydroicaritin showed notable antibacterial effects [46]. These findings demonstrate that Epimedium possesses significant anti-inflammatory, antibacterial, and antiviral functions. Inflammaging is now considered a contributing factor in chronic diseases, including Parkinson's disease, Alzheimer's disease (AD), atherosclerosis, and type 2 diabetes. Therefore, Epimedium may hold potential in preventing these age-related conditions.

The regulation of sex hormones

Sex hormones are closely linked with the aging process. In men, steroid hormone levels correlate positively with age [56], and the rate of hormonal changes may serve as an indicator of healthy aging [57]. In women, declining ovarian function during menopause contributes to vascular aging [58]. Estrogens have neuroprotective properties, and reductions in estrogen levels may be associated with neurodegenerative disorders [59]. Sex hormone levels also influence sexual function, yet age-related sexual dysfunction is still poorly studied in both sexes [60–62]. In Traditional Chinese Medicine, Epimedium—literally meaning "high libido"—has long been used to enhance male sexual function and treat infertility. TCM theory attributes sexual dysfunction primarily to kidney deficiencies.

Epimedium is believed to improve kidney function, thereby enhancing sexual performance, and may be used alongside Western treatments in clinical settings.

Age-related declines in psychological, physical, and sexual functions in men are partly attributed to reduced testosterone levels [63, 64]. Clinical manifestations in older men can be broadly divided into sexual and nonsexual categories [64]. Nonsexual symptoms include lower energy or motivation, mood disturbances such as sadness, impaired concentration and memory, reduced muscle mass, increased fat deposition, and decreased work efficiency [65, 66]. Sexual symptoms primarily involve erectile dysfunction (ED), reduced libido, decreased frequency of sexual desire, and fewer nocturnal erections [48, 67]. ED, defined as the inability to achieve or sustain an erection sufficient for satisfactory sexual activity, is prevalent among older men [68]. Besides advancing age, key contributors to ED include smoking, obesity, diabetes, hypertension, and depression [69, 70]. Effective, safe, and standardized therapies for ED remain limited [69, 71, 72]. Complementary approaches, including herbal remedies and acupuncture, have gained increasing popularity worldwide. Epimedium may act as a potential phosphodiesterase type 5 (PDE5) inhibitor [73, 74].

Males

Two clinical trials examining Epimedium's effects on aging male symptoms were identified through PubMed. A 2013 randomized, double-blind, placebo-controlled crossover study in Thailand evaluated a herbal formulation containing Epimedium for ED [75]. Sixty-one adult males with mild to moderate ED were randomly assigned to receive either the herbal preparation or a visually identical placebo for two weeks, followed by a one-week washout and then crossover to the other treatment [75]. The International Index of Erectile Function (IIEF) questionnaire, assessing erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction, was used to measure outcomes [75]. Scores collected at baseline and after each treatment indicated that the herbal medicine improved IIEF scores across all domains compared with placebo, with statistically significant improvement observed only in erectile function [75]. Another open-label randomized trial in Japan compared Epimedium with a Kampo preparation approved for reimbursement but distinct from TCM Epimedium [76]. Forty-nine aging men with mild to severe symptoms were assigned to either group for six months. Participants receiving Epimedium experienced greater improvement in somatic and psychological aging markers, including ED, compared with baseline and the Kampo group [76].

Females

Each year, around 1.5 million women experience symptoms associated with the menopausal transition, including vasomotor disturbances, vulvovaginal atrophy, sleep difficulties, and mood changes [77, 78]. Estrogen therapy has been shown to alleviate vasomotor and sexual symptoms but carries increased risks of breast cancer, stroke, venous thromboembolism, and endometrial cancer [77, 79]. In Asia, Epimedium is widely used as an alternative therapy to relieve menopausal symptoms by supporting renal and hepatic function, consistent with TCM principles. Only one clinical study investigating Epimedium in menopause was identified via PubMed [80]. Ninety women were randomized to either a six-month course of Epimedium water extract or a six-month placebo control. The results demonstrated that Epimedium significantly increased serum estradiol levels ($p < 0.01$) [80].

Efficacy

Clinical trials suggest that Epimedium may improve sexual and menopausal symptoms. However, most studies are limited by small sample sizes and a lack of large-scale, multicenter, randomized controlled trials.

Sexual function

Epimedium has shown potential in enhancing sexual health. In a Chinese study, Zhuang analyzed 20 middle-aged men with ED, dividing them into treatment and control cohorts. The treatment group received anhydroicaritin (AHI), a compound derived from Epimedium, and results suggested that AHI provided clinical benefits in managing ED among these men ($P > 0.05$) [81]. Another trial enrolled 61 adults with mild to moderate ED who were randomly assigned to either an Epimedium-containing herbal formulation or a visually identical placebo. Participants received the active treatment for two weeks, followed by a one-week washout, and then switched to the alternative treatment for an additional two weeks [75]. The International Index of Erectile Function (IIEF) was used to assess outcomes, and scores collected before and after each treatment indicated a general improvement across all domains with the herbal therapy, with statistical significance noted in erectile function [75]. A six-

month study in Japan involving 49 older males reported that Epimedium led to superior improvements in somatic and psychological aging markers, including ED, compared with baseline measurements and a Kampo-treated group [76]. Beyond oral administration, a topical Epimedium preparation (3% peppermint oil, 30% ICA) was found to reduce penile sensitivity, provide localized anesthetic effects, and offer therapeutic benefit for premature ejaculation [82].

Osteoporosis

Evidence also supports Epimedium in preventing bone loss and managing postmenopausal osteoporosis. In Hong Kong, China, a 24-month randomized, double-blind, placebo-controlled trial with 100 postmenopausal women evaluated the effect of Epimedium-derived phytoestrogen flavonoids (EPFs) on bone mineral density (BMD) [8]. Another multicenter study in Mainland China followed 194 postmenopausal women for 5 years, comparing kidney-tonifying herbal Fufang with phytoestrogenic Epimedium (n = 101) against placebo (n = 93) [47]. After 5 years, the Fufang group experienced significant BMD gains, whereas BMD decreased in the placebo cohort ($p < 0.05$). Fracture risk in the Fufang group was reduced, with a relative risk of 0.57 ($p < 0.05$) [47]. EPFs maintained BMD at 12 and 24 months, while reductions occurred in the control group, with significant differences between groups. No notable changes were observed in serum estradiol or endometrial thickness. Additionally, Epimedium applied topically as the primary component of a medicinal cake improved clinical symptoms in elderly osteoporosis patients, enhanced BMD, and lowered serum β-type I collagen carboxy-terminal peptide [39].

Coronary heart disease

Atherosclerosis underlies most ischemic cardiovascular and cerebrovascular conditions. In a study of 120 elderly patients with kidney deficiency syndrome and ischemic cardiocerebral vascular disorders (60 with coronary heart disease, 60 with cerebral atherosclerosis), treatment with Epimedium compound granules was administered [83]. Post-treatment, the overall effectiveness and marked effectiveness rates in the treatment group were 96.7% and 39.5%, respectively. Improvement in ECG readings was observed in 70% of coronary heart disease patients, while EEG improvement was noted in 75% of cerebral arteriosclerosis cases. Treatment also led to reductions in serum cholesterol and total cholesterol (TC) levels, while HDL-C concentrations increased. Serum SOD activity rose, and MDA levels decreased. Outcomes were superior to those in a control group treated with Su-Guan-Bian. Mechanistic studies suggest Epimedium compound granules exert benefits by lowering lipid levels, scavenging free radicals, and modulating the prostacyclin I2 to thromboxane A2 (TXA2/PGI2) ratio, contributing to prevention and therapy of atherosclerosis.

Adverse reactions

Even though Epimedium is classified as both a dietary and medicinal product, it cannot be considered completely risk-free. Recent research has documented potential adverse effects of Epimedium and its formulations, though no severe side effects have been consistently reported. One study assessed the safety of Epimedium water extract and determined its LD50 to exceed 80 g/kg. The IC50 values were 55.4 mg/ml in Chinese hamster ovary cells and 19.53 mg/ml in lung cells. Additionally, all conducted toxicity assays yielded negative results [84]. Long-term toxicity was also evaluated using a standard Wistar rat model, where a dose of 410 g/kg/day was administered for 12 weeks without inducing notable pathological changes [85]. Genotoxicity testing confirmed that the water extract of Epimedium is nongenotoxic [86]. In animal studies examining adverse drug reactions, mice treated with Epimedium for three days exhibited vomiting, reduced appetite, and decreased activity [84]. Prolonged administration for 15 days resulted in fatty liver changes. Given that Epimedium exhibits androgen-like effects and androgens are associated with hepatotoxicity, it is reasonable to infer that Epimedium may possess some hepatotoxic potential [87].

Application status of Epimedium

Currently, nearly all clinical research on Epimedium has been conducted in Asian populations, predominantly in China. The limited number of studies published in English reduces the generalizability of findings. There is a need for rigorously designed and executed clinical trials to validate the therapeutic effects of Epimedium in broader clinical contexts. **Table 1** presents an overview of the current clinical investigations involving Epimedium. Although large-scale, high-quality trials remain scarce, promoting global interest in Epimedium as a natural anti-aging agent is a key objective.

Table 1. Summary of clinical trials of Epimedium.

Clinical Trial	Study Design	Study Population	Sample Size	Formulation	Dosage	Reported Efficacy	Reported Safety
Zhang *et al*., 2007 [8]	RCT	Healthy postmenopausal women (mean age 64 y)	100	Capsule containing 15 mg Icariin	4 capsules daily	Showed positive effects in slowing bone loss	No major systemic side effects or abnormal hematologic findings
Deng *et al*., 2012 [47]	RCT	Postmenopausal women with osteoporosis (47–70 y)	194	Herbal Fufang	10 g/day, twice per day	Demonstrated protective benefits against bone loss	No significant adverse reactions noted
Punyawudh *et al*., 2013 [75]	Randomized, double-blind, placebo-controlled crossover study	Patients ≥18 y with mild or mild-to-moderate ED	63	Tablet containing Epimedium Drevicornum Maxim 120 g	1 tablet taken 1 hour prior to sexual activity	Improved mild-to-moderate ED symptoms	Dizziness (13.3%), facial numbness (1.6%), tachycardia (1.6%)
Nishimatsu *et al*., 2014 [76]	RCT	Male subjects with mild or moderate aging-related symptoms (mean age 63 y), including ED	94	Capsule with 5 mg Epimedium herb extract	1 capsule twice daily	Alleviated aging symptoms including ED	Epigastric discomfort (4%) and skin rash (4%)
Yan *et al*., 2008	RCT	Healthy postmenopausal women (mean age 57 y)	90	Herba Epimedii water extract	300 mL daily	Lowered TC and TG levels; elevated serum E2	No serious adverse events observed
Zhao *et al*., 2012	RCT	Patients with stable moderate–severe COPD (58–90 y)	90	30 g ShanYao with 12 g Herba Epimedii; soaked 30 min, decocted twice, filtered	80 mL twice daily	Improved dyspnea, exercise tolerance, and quality of life	No major adverse events reported
Cai *et al.*, 1998	RCT	Patients receiving prednisone (age not specified)	65	EB 5 g	5 g daily	EB reduced neuroendocrine–immune suppression caused by glucocorticoids	Not reported
Liao *et al.*, 1995	Controlled trial	Maintenance hemodialysis patients (age not specified)	34	ES	0.6 g/kg daily	Showed therapeutic benefits for sexual dysfunction and immune insufficiency	Not reported

RCT: randomized controlled trial; ED: erectile dysfunction; TC: cholesterol; TG: triglyceride; E2: serum estradiol; EB: Epimedium brevicornum; ES: Epimedium sagittatum; COPD: chronic obstructive pulmonary disease.

Conclusion

Diseases associated with aging now represent a significant burden for global public health. While Western medicine has made notable strides in developing anti-aging interventions, natural remedies—particularly Chinese herbal medicine—have created a distinct therapeutic system rooted in traditional Chinese medical principles. These approaches provide rationale-based strategies for managing a variety of age-related conditions. Among these, Epimedium species have been widely employed in TCM to enhance sexual function, strengthen immunity, and delay aging processes. Flavonoids and polysaccharides have been identified as the primary bioactive compounds responsible for these effects.

This review summarized the underlying mechanisms of Epimedium's anti-aging effects and collated evidence from randomized controlled trials evaluating its efficacy and safety. Certain studies have highlighted the anti-aging properties of Epimedium flavonoids (EF) and icariside (ICA). Adverse reactions reported in clinical trials were also reviewed, with discussion of potential causes.

Typical clinical dosages of Epimedium range from 250 to 500 mg, although the optimal therapeutic dose has not yet been established. Major contraindications appear limited, but evidence regarding long-term safety is still insufficient. In TCM, Epimedium is considered a kidney Yang tonic, and its hormone-like effects may contribute to side effects that warrant further study. Modern pharmacological investigations into EF and ICA have advanced understanding of its mechanisms. At present, Epimedium is commonly used in China for managing age-related diseases in clinical practice. However, additional large-scale and rigorously designed studies are necessary to refine its use and fully establish clinical guidelines.

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