

**Indications**

Menopausal symptoms; general female reproductive health; support of bone, hair, and fingernails; sexual longevity including vaginal lubrication; and enhanced breast size.

**Mechanism of Action**

*Pueraria* contains numerous isoflavones that are phytosterols, plant compounds with steroid-like effects. The phytosterols include β-sitosterol, coumestrol, genistein, daidzein, formononetin, puerarin, and miroesterol. Miroesterol is a stable phytosterol credited with many tissue-rejuvenating effects, and it may be used as a biomarker for kudzu quality.

*Pueraria* has been shown to act on both alpha (ERα) and beta (ERβ) estrogen receptors. In general, ERα receptors direct cellular proliferation, whereas the ERβ subtype directs differentiation and apoptosis. ERα are more active early in the fetal and neonatal periods, whereas ERβ subtype dominates in puberty and adulthood. When the balance between ERα and ERβ receptors is disrupted, reproductive health may be impaired. The phytoestrogens miroestrol and coumestrol act on both ERα and ERβ receptors, whereas daidzein and genistein are more active on ERβ receptors. Miroestrol blocks excessive stimulation of ER receptors in cases of breast or endometrial cancer, yet acts as an estrogen agonist to support cardiovascular health and alleviate menopausal symptoms. Deoxymiroestrol, which is probably more active than miroestrol, has similar cellular and clinical effects.

The phytosterol formononetin up-regulates the expression of ERβ without stimulating ERα in endometrial and vaginal cells of ovarectomized rats. Formononetin has intramembranous ossification effects in traumatized mice bones. This effect is comparable to that of parathyroid hormone administration. Formononetin decreases metabolic activity in osteoarthritic osteoblasts while markedly increasing metabolic activities in normal osteoblasts. Formononetin has a greater remodeling effect on osteogenic markers and inflammatory cytokines in osteoarthritic bone than in normal bone.

Although one study reported puerarin to have little to no binding of ERα and ERβ receptors in bone, other studies have reported ER agonism that contribute to *Pueraria*’s bone-building effects. In one study, puerarin stimulated osteoprotegerin, inhibited receptor activator of nuclear factor-κB ligand, and suppressed interleukin-6 production by human osteoblastic cells via agonism at both ERα and ERβ. *Pueraria* retards bone absorption without interfering with overall bone metabolism and stimulates bone regeneration without having proliferative effects on the endometrium. *Pueraria* promotes alkaline phosphatase and osteoprotegerin, decreases osteoclastogenic factors, inhibits bone absorption by osteoclasts, and stimulates proliferation and especially differentiation of osteoblasts. In total, these mechanisms promote bone gain. Formononetin also improves trabecular microarchitecture, collagen
synthesis, and osteoprotegerin activation without exerting proliferative effects on the endometrium, and it has only weak proliferative effects on the breast epithelia.

Puerarin prevents the increase in β-amyloid caused by estrogen deficiency. In the hippocampus, puerarin increases choline acetyltransferase activity and expression.

Pueraria extracts have been used topically to treat postmenopausal vaginal atrophy and in skin products for cosmetic effects. One study on postmenopausal macaques has shown kudzu to significantly mature the vaginal epithelium without causing systemic side effects. A 12-week randomized controlled study of postmenopausal women significantly improved the vaginal maturation index, decreased adverse vaginal symptoms, and was comparable to conjugated equine estrogen cream.

Evidence-Based Research

Numerous animal and human clinical trials as well as many molecular and tissue culture studies support the use of Pueraria for menopausal symptoms and to support the skin, vaginal mucosa, bones, brain, and cardiovascular system in the postmenopausal decades. One double-blind, placebo controlled clinical trial found Pueraria to retard or prevent the development of gray hair. Pueraria may reduce the risk of cerebrovascular disease that accelerates in postmenopausal women. Animal studies have shown that follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels decrease with Pueraria supplementation, suggesting negative feedback from increased hormonal status of the tissues. Several small clinical studies dosed symptomatic perimenopausal women with either 50 or 100 mg of Pueraria mirifica for 6 months and reported improvements in the Greene climacteric scale of menopausal symptoms associated with slight increases in serum estradiol.

Pueraria has supportive effects on bone density and reduces postmenopausal thinning of the bones. Formononetin has been shown to prevent ovariectomy-induced osteopenia in rats as well as having therapeutic and restorative effects on osteopenia. Formononetin may be a safe hormone-like therapy for osteoporosis. One human randomized clinical trial found Pueraria extracts of 20, 30, or 50 mg to exert estrogen-like effects on bones without exerting a proliferative effect on the endometrium, as evidenced by a decrease in bone-specific alkaline phosphatase compared with placebo.

Pueraria has positive effects on blood lipids. A recent study on ovariectomized rats showed that isoflavones from Pueraria roots inhibited loss of bone density and lipid elevation. Both animal and human studies have shown kudzu isoflavones to reduce lipid elevations and accumulation of abdominal fat that may follow rapid declines in estrogen levels. A small clinical trial compared Pueraria to placebo on serum lipids of postmenopausal women. After 2 months, high-density lipoprotein was 34% higher and low-density lipoprotein was 17% lower in the group receiving Pueraria.

A double-blind, placebo controlled human trial examined the effects of Pueraria on blood lipids, bone alkaline phosphatase, and endometrial thickness and breast parameters in postmenopausal women aged 45–60 years. After 6 months, the groups receiving Pueraria showed a significant decrease in bone alkaline phosphatase, suggesting a reduction in bone resorption and turnover. No measurable changes were seen in the breasts or the endometrium, suggesting that it does not have a proliferating effect on the uterine lining or breasts.

A phase III clinical trial compared Pueraria to conjugated equine estrogen on perimenopausal symptoms and serum hormone levels. All groups showed comparable relief of vasomotor, urogenital, and
psychological symptoms. No significant differences in FSH, LH, or serum estradiol levels were seen between the groups. Thus, *Pueraria* was as effective as conventional pharmaceutical therapy.\(^{27}\)

### Safety in Pregnancy and Breastfeeding

*Pueraria* has a folk lore reputation as an emmenagogue and a contraceptive agent and therefore should be avoided during pregnancy unless clinical trials prove otherwise. Puerarin crosses the placental barrier and has endocrine-disrupting effects in rats.\(^{28}\) Significant antifertility activity of *Pueraria* has been demonstrated in laboratory animals. Puerarin at ≥300 mg/kg/day for days 1–2 postcoitus results in complete implantation failure because of effects on endometrial ERα and ERβ and disrupted implantation in rats.\(^{29,30}\) *Pueraria* seems to have no impact on male fertility or the hypothalamus–pituitary–testis axis, although in mice doses of 100 mg/kg have been shown to reduce epididymis and seminal vesicle weights and to reduce the sperm motility and viability.\(^{31}\) A study on isolated sperm showed that using puerarin reduced the spontaneous acrosome reaction of spermatozoa, whereas *Pueraria* reduced sperm motility.\(^{32}\) Sprague–Dawley rats were given testosterone to induce prostate hyperplasia and then daidzein and genistein for 30 days with finasteride as the positive control. The *Pueraria* extract reduced the size of the hyperplasia-induced prostate and significantly improved the architecture of the prostate cells.\(^{33}\)

### General Safety

A mouse and rat toxicity study evaluated the acute and subchronic toxicity effects of 5 g/kg body weight of *Pueraria* flower extract and reported no mortality or toxicological changes during the experimental period.\(^{34}\) There was one anecdotal report from Seoul, South Korea, of a middle-aged female who developed acute interstitial nephritis diagnosed by renal biopsy after the ingestion of *Pueraria* root juice for 10 days. After discontinuing the juice, symptoms completely resolved.\(^{35}\)

Current evidence suggests that *Pueraria* is safe for women with existing or a history of breast and uterine cancer. Puerarin, the major isoflavone, has been shown to decrease the overexpression of ERs.

Puerarin may inhibit hepatic cytochrome P450-mediated drug metabolism in rats and humans, so interactions with some drugs are possible.\(^{36}\) A rat study that administered 4.0 and 2.0 g/kg of *Pueraria* root decoction with methotrexate caused 57.1% mortality in the 4.0-g group and 14.3% mortality in the 2.0-g group and increased the half-life of methotrexate by 53.9% and slowed the clearance by 47.9%.\(^{37}\) Methotrexate requires CYP450 2E1 for metabolism. A study of *Pueraria* extract on rabbit and human liver supersomes found an ethanol extract had more effect than puerarin 2E1, 1A2, and 2C9 enzymes, but it concluded that the herb was safe for human consumption.\(^{38}\)

### Dosage

Dosages of 20 mg to 2.4 g/day have been used in most of the human clinical studies. Topical doses have been 0.5–1.0 g/day.

### Traditional Uses

*Pueraria* species are referred to as kudzu or Japanese arrowroot in North America. The vine is native to southern Japan and southeastern China, but it was introduced to India and North America for erosion control where it now grows prolifically, covering everything in its path. The roots have been used in Oriental medicine for centuries and in classic antiaging and rejuvenation formulas in Thailand. Kwoa
khruea is the common name used for rejuvenating herbs in Thailand and white kwao khruea or *Pueraria candollei* is especially indicated for female rejuvenation; menopausal symptoms; facial rejuvenation; support of the bone, hair, and fingernails, and it is sometimes claimed to support sexual longevity including vaginal lubrication and enhanced breast size.

*Pueraria* is credited with many medicinal uses including hepatoprotective effects; alcohol protection; reduction in alcohol consumption and craving; neuroprotective, cardioprotective, anti-diarrheal, and activity against acute dysentery; and for treatment of deafness, tinnitus, and vertigo. It is also credited with optimizing metabolism and is reported to have antidiabetic, insulin-enhancing, and antiobesity effects.

*Pueraria lobata* is historically used in combination with *Salvia miltiorrhiza* and *Angelica* species for cardiotonic effects including circulatory-enhancing, anti-inflammatory, anti-ischemic, and antiatherogenic effects.

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