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Efficacy and safety of *Pueraria candollei* var. *mirifica* (Airy Shaw & Suvat.) Niyomdham for menopausal women: A systematic review of clinical trials and the way forward

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ABSTRACT

Ethnopharmacological relevance: *Pueraria candollei* var. *mirifica* (Airy Shaw & Suvat.) Niyomdham (commonly termed *P. mirifica,* PM) growing in upland Thailand has a long history as a postmenopausal rejuvenant therapy for indigenants. Its amelioration of menopause symptoms in clinical trials was assessed.

Materials and methods: International and Thai databases were searched from inception to February 2017. Clinical trials investigating effects of PM menopausal or postmenopausal women were included. Outcomes were self-reported menopausal symptoms, serum reproductive hormones, urino-genital tract function, and bone surrogates. Methodological quality was assessed by Cochrane risk-of-bias v2.0, and a 22-parameter quality score based on the CONSORT checklist for herbal medicines.

Results: Eight studies (9 articles) used data from 309 menopausal patients. Five-studies demonstrated that PM was associated with climacteric scores reduced by ~50% compared to baseline. Other PM studies using limited numbers of placebo participants suggested improved vaginal and other urogenital tract symptoms. Bone alkaline phosphatase halved (suggesting lowered bone turnover). Variable serum reproductive hormone levels suggested menopausal status differed between studies. PM active ingredients and sources were not defined. Adverse event rates (mastodynia, vaginal spotting, dizziness) were similar in all groups (PM, conjugated equine estrogen, and placebos) but serum C-reactive protein doubled. These studies had design and reporting deficiencies, high risks of biases, and low quality scores.

Conclusions: The efficacy of PM on menopausal symptoms remains inconclusive because of methodological short-comings especially placebo effects inherent in self-assessment/recall questionnaires and no PM standardization. PM efficacy and safety need a fundamental re-appraisal by: (i) cohort (retro- and prospective) studies on current users to define its traditional use for rejuvenation; (ii) tightly coupling long-term efficacy to safety of well-defined PM and multiple end-points; (iii) using study design related to current understanding of menopause progression and estrogen pharmacology (iv) robust pharmacovigilance.

Abbreviations: CEE, conjugated equine estrogen; MPA, medroxyprogesterone acetate, MGCS, Modified Greene Climacteric Scale; FSH, follicle stimulating hormone; LH, luteinising hormone; ERα, estrogen receptor-α; HRT, hormone replacement therapy

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1. Introduction

For many middle-aged women, cessation of ovarian function causes intolerable menopausal symptoms including vasomotor dysfunction (hot flushes, sweating), sleep disorders (insomnia, waking and erratic sleep), depression, sexual dysfunction (reduced libido, urogenital disorders), and musculoskeletal pain. Vasomotor symptoms affects 57% of women, begins before menopause and continues for 1 to > 15 y (mean 4.5 y), but is shorter in Asians, and more prolonged in African Americans, the obese, premature menopaused, and the stressed (Avis et al., 2015). Estrogen replacement is the rational treatment but the 2002/3 Women Health Initiative (Rossouw et al., 2002) and Million Women studies (Beral and Collaborators, 2003) reported adverse events as major risks, including thrombosis, neoplasms and vascular events. But re-analyses and sub-analyses have qualified the head-line conclusions and better identified the women who could benefit from hormone treatment. Continuation of the trials is providing streams of new data. Prescription rates had plummeted and continue to be much reduced. Women were left with several alternatives including (i) bio-identicals (ii) non-hormonals to treat symptoms (eg antidepressants), (iii) lifestyle changes, and (iv) phytoestrogens which need no prescription.

Legumes commonly express isoflavones and the more potent estrogenics, coumestrols. *Leguminosae Pueraria* genus comprises 15–20 species that are invasive woody climbing perennial beans indigenous to south-east Asia but genetically diverse (Egan et al., 2016). They are used for fodder (foliage), human food and medicines (tubers)(Keung, 2003). Several varieties and cultivars been studied for their estrogenicity, especially *Pueraria candollei* var. *mirifica* (Airy Shaw & Suvat.) Niyomdham (commonly termed *P. mirifica*, or in the Thai language, kwao khrua khaw (various spellings). It is restricted to a few deciduous hilly jungles in north and western Thailand (Kashemsanta et al., 1952; Niyomdham, 1992) but has been over-exploited and become endangered. Accordingly, it is extensively farmed for medicines.

Traditional uses of *P. mirifica* emphasised rejuvenation and good health in older women, that include an increasing ability to work, preventing infection, promoting healthy skin and hair growth, improving cognitive function, lessening mammary ptosis, improving sleep, blood 'tonic', but contra-indicated for younger adults (Cain, 1960; Schauss, 2001; Suntara, 1931). These indigenants appear to have recognised its pleotropic actions in old age without knowledge of hormones in that era. With more advances in current practice, these are commonly recognised as menopausal symptoms in late mid-life women. These changes accord with currently appreciated postmenopausal functional changes including increased cardiovascular risks, bone degeneration, cognitive decline, metabolic disease, immune attenuation, and deterioration of skin and hair.

P. mirifica, especially its tubers contain glycosides of genistein, and daidzein, the rare puerarin and mirificin, the unique kwakhurin and mirificoumastans (Keung, 2003), and notably miroestrol and its congeners. These miroestrols are potent estrogen agonists *in vitro* and in animals (Benson et al., 1961; Chansakaow et al., 2000). Pre-clinical studies suggest that miroestrols are responsible for the major clinical actions (Malaivijitnond, 2012). In women with amenorrhea, 1 or 5 mg/day oral miroestrol for 2–3 weeks produced estrogenic vaginal actions after which withdrawal induced endometrial bleeding, actions that are compatible with estrogen receptor-α (ERα) agonists (Cain, 1960). There were noteworthy estrogen-type adverse events suggesting the doses were excessive.

Early studies standardized *P. mirifica* preparations by HPLC of isoflavones whose total contents varied 50-fold between season, cultivar, and region (Cherdshewasart and Sriwatcharakul, 2007). Similar wide variations were found using bioassay (rat vaginal cornification) in *P. mirifica* sampled by province (Cherdshewasart et al., 2008). Miroestrol in *P. mirifica* also varied by region and variety (Kitisripanya et al., 2017). In commercial *P. mirifica* products, oxymiroestrol concentrations varied ~70-fold (Yusakul et al., 2013) and some formulations contained no *P. mirifica* (Maruyama et al., 2014). Genomic studies have detected sequence differences in batches of *P. mirifica* (Bunmanop et al., 2011; Wiriyakarun et al., 2013) which may contribute to content inconsistencies.

Currently, *P. mirifica* products are globally promoted for breast enlargement, cosmetics, and menopausal symptoms (Googling for 'pueraria' yields results dominated by *P. mirifica treatments*). Purveyors of *P. mirifica* cite relevant clinical trials in glowing terms to support its efficacy; many products carry appropriate warnings while others declare it as "completely safe". Furthermore, internet blogs on *P. mirifica* reveal many consumers using 10× recommended doses in an attempt to titrate an effective dose regime. Clearly, users need an independent and unbiased assessment of *P. mirifica* through a systematic review enabling them, or their medical practitioners, to make an informed risk/benefit analysis. Such a review appears not to have been undertaken and is therefore timely. Accordingly, we have conducted this systematic review to evaluate the clinical efficacy and safety of *P. mirifica* to alleviate menopausal symptoms in order to create a safer and reproducible clinical profile.

2. Materials and methods

This systematic review was conducted according to the Cochrane Collaboration framework guidelines (Higgins and Green, 2011), and reporting followed the PRISMA Statement (Moher et al., 2009).

2.1. Search strategies and study selection

The following databases were searched for original research articles from their inception to February 2017: AMED, CINAHL, Cochrane Central Register of clinical trials, EMBASE, Health Science Journals in Thailand, PubMed, Thai Index Medicus, Thai Library Integrated System, Thai Medical Index, Thai Thesis Database, WHO registry, and www.clinicaltrial.gov. Strategic search terms used scientific and common synonyms of *Pueraria candollei* var. *mirifica* (Airy Shaw & Suvat.) Niyomdham, *P. mirifica* or "kwao krua kao" (the Thai name). Reference sections of all retrieved full articles were reviewed for potential studies not indexed in the above databases.

Clinical studies were included if they met the following inclusion criteria: 1) conducted on humans; 2) investigated therapeutic effects of *P. mirifica* on menopause. CK screened all the titles and abstracts to determine whether the studies assessed the therapeutic effects of *P. mirifica*. Full-text articles of the potential studies were reviewed by CK and NS; then the included studies were subsequently reviewed by CK, NS, and TD. When uncertainties regarding the eligibility occurred, they were resolved by discussion.

2.2. Data extraction

Data extraction was undertaken by CK using a data extraction form and cross-checked by TD and CNS according to the CONSORT statement for reporting herbal medicinal interventions (Gagnier et al., 2006). The data extracted and reported included: study design; number and characteristics of participants; age of participants; herbal preparations; standardization of preparations; treatment protocols; and outcomes. Outcomes of interest related to menopause were menopausal symptoms; plasma estradiol and FSH/LH; and adverse events.

2.3. Quality assessment of included studies

The studies were assessed for methodological quality by CK, CNS, and TD using the Cochrane revised tool for risk of bias tool (RoB 2.0) for individually randomized, parallel group trials (Higgins and Green, 2011). This tool assesses biases due to randomization process; to deviations from intended intervention; missing outcome data; outcome measurements, selective reported of results, and overall bias. Each