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Review

Red clover extract for alleviating hot flushes in postmenopausal women: A meta-analysis

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ABSTRACT

The safety and efficacy of red clover for alleviating menopausal hot flushes are yet to be established. The aim of this meta-analysis was to generate evidence from published literature regarding red clover as a treatment option for menopausal hot flushes. The results showed that red clover when compared to placebo was effective in reducing menopausal hot flushes when administered for 3–4 months (MD = −1.34, 95% CI = −1.90 to −0.77, $p < 0.00001$), but their effect did not persist at 12 months (MD = 0.89, 95% CI = −0.07 to 1.85, $p = 0.07$).

Contents

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1. Introduction

Approximately 70% of women experience symptoms associated with menopause presenting as hot flushes, sweating, palpitations and insomnia [1]. Two-thirds of postmenopausal women experience hot flushes, with 10–20% of all postmenopausal women experiencing intolerable symptoms [2]. The most plausible theory of aetiology so far is the decline in oestrogen concentrations, leading to instability of the hypothalamic thermoregulatory setpoint [3].

Hormone therapy (HT) is the most effective treatment for hot flushes [4]. However, the use of the HT increases the risk of hormone-dependent cancers, such as those of the breast, and endometrium. Other side-effects include breast tenderness, fluid retention, and a heightened risk of thrombosis [5]. Safety concerns over hormonal products have led to the popularisation of many complementary treatments, such as red clover extract.

Red clover extract (*Trifolium pratense*) is a rich source of isoflavones, plant-based chemicals that produce oestrogen like effects in the body. Red clover extract contains compounds that are metabolised to genistein and daidzein after consumption [6,7]. It is widely used in many forms of traditional medicine including Ayuvedic medicine, Chinese medicine and by the Cheerokes of North America. Red clover extract is used to reduce many of the discomforts plaguing menopausal women, however there has been controversy regarding its efficacy [8].

To date, there is insufficient clinical evidence to support the efficacy of red clover extracts for alleviation of menopausal hot flushes. Findings from clinical trials are still inconclusive and inconsistent between studies. This review and meta-analysis thus aimed to document and update evidence from published literature regarding efficacy of red clover extract as a treatment option for menopausal hot flushes.

2. Methods

This review was conducted according to Cochrane guidelines [9]. Randomised or quasi-randomised trials were considered without any restriction on the publication date and language. All trials that had used red clover extracts (mono/single preparation) and that have compared treatment with placebo were included. Studies that included women with breast cancer were excluded as many women with breast cancer use tamoxifen, which can itself cause hot flushes. Studies were ineligible if they included women who were: on hormone therapy; vegetarian (consuming 10 g of legumes per day or more); taking phytochemical herbs, soy and soy products; consuming more than 2 units of alcohol per day; using isoflavone enriched products in the last 16 weeks; anti-depressants users; and women with other medical conditions. The comparison of interest was placebo.

Average daily frequency of hot flushes compared with baseline was defined as the primary outcome measure. The secondary outcomes were other menopausal symptoms scores, quality of life and adverse events of the treatment.

2.1. Search methods for identification of studies

According to the Cochrane Menstrual Disorders and Subfertility Group, recommended databases such as Ovid MEDLINE(R) (1946 to present date), EMBASE (1980 to May 4, 2010), CENTRAL and AMED (Allied and Complementary Medicine; 1985 to October 2013) were searched. The last search was done on 10th October 2013. Synonyms of red clover were used for search purposes. Red clover was searched as *T. pratense*, cow clover, meadow clover, purple clover, red clover, trefoil, wild clover, promensil (a brand name of red clover extract). Isoflavone was searched asirilone, pratensein, formononetin, biochanin A, daidzen, genistein and phytoestrogen. Since the aim was to identify hot flushes related to menopause, the search terms were combined as hot flush and menopause. For menopause, perimenopause, premenopause, postmenopause and climacteric were used.

2.2. Data collection and analysis

The data collection and selection process were done by both authors (P.G. and M.M.H.) independently. The final list of included texts was reached by consensus.

The change from baseline to endpoint in hot flushes frequency was used to assess differences between the active treatment and the placebo group. Mean difference (MD) and 95% confidence intervals (CIs) were calculated using standard meta-analysis software (Revman 5.2) that uses the inverse of the variance to assign weight to the mean of the within-study treatment effect [10]. Summary estimates were calculated using a random effects model. The chi-square test for heterogeneity was performed to determine whether the distribution of the results was compatible with the assumption that inter-trial differences were attributable to chance variation alone. Due to the limited number of included studies, we were unable to assess publication bias. Sensitivity analysis was performed to test the robustness of the results.

2.3. Data extraction and management

Data relating to characteristics of women, study design, intervention and control group, drugs/dose/day, duration of treatment (months), baseline and end line hot flushes per day for treatment and control group were extracted according to our predefined criteria using the data entry form. The form was initially prepared by the authors, piloted by entering data from one of the included studies and then finalised. The data were extracted independently by two reviewers P.G. and M.M.H. Clarification was sought from corresponding authors of included studies where necessary.

2.4. Assessment of risk of bias in included studies

Risk of bias appraisal was independently conducted by both authors using the Cochrane risk-of-bias tool [11,12].