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Original Article

Effect of Herbal Medicine on Vaginal Epithelial Cells: A Systematic Review and Meta-analysis

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Objectives: The present meta-analysis aimed to assess the effect of the herbal medicine on the vaginal epithelial cells (VECs) among the menopausal subjects.
Methods: The literature related to VECs exposed to various herbal medicines in menopausal women were searched on three databases, MEDLINE (1966-August 2017), Scopus (1990-August 2017) and Cochrane Library (Cochrane Central Register of Controlled Trials; 2014).
Results: Totally, the meta-analysis was conducted on 11 randomised controlled trials. Based on the findings, the standardized mean difference (SMD) of maturation value (MV) was observed to be elevated by 0.48% (95% interval confidence [CI], 0.108-0.871; $P = 0.012$), as well as the heterogeneity was high ($I^2 = 84\%$; $P < 0.001$). The MV revealed a significant increase in soy group (SMD, 0.358; 95% CI, 0.073-0.871; $P = 0.014$) compared to the control group.
Conclusions: The herbal medicines exhibited a statistically significant effect on the VECs. A significant effect on the VECs was also found in the subgroup analysis of the patients, who received soy. However, further and extensive studies are required to achieve reliable outcomes. **(J Menopausal Med 2018;24:11-16)**

Key Words: Atrophic vaginitis · Menopause · Phytoestrogens

Introduction

Menopause is a natural biological transition in life experienced by all women as they age,[1,2] which is caused by end of ovarian function resulting in permanent discontinuation of the menstrual cycle.[3,4] Women live a third of their life in the period of menopause.[5]

Some of the respective consequences following the menopause characterized by estrogen deficiency are vaginal atrophy, bone loss, mood and flashes.[6] The quality of life of the postmenopausal women is affected by Genitourinary syndrome[7] whose symptoms though are attenuated widely by hormone therapy. Reportedly, there are several complications following the hormone therapy, including high risk of breast cancer, endometrial cancers,[8] breast tenderness and venous thromboembolism.[9] Therefore, the herbal medicines nowadays have attracted further attentions as safe alternatives by many postmenopausal women.[10] To the best of our knowledge, limited studies investigated the effect of herbal medicine on vaginal atrophy among menopausal women and there are some new published trials. Accordingly, it is essential to update the knowledge through the systematic review or meta-analysis in this regard.

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Materials and Methods

1. Study design

The literature concerning the vaginal epithelial cells (VECs) exposed to various herbal medicines in menopausal women was searched on three databases of MEDLINE (1966-August 2017), Scopus (1990-August 2017) and Cochrane Library (Cochrane Central Register of Controlled Trials; 2014).

The keywords for searching were the relationship between menopause and primrose oil, St. John's wort, Hypericum-perforatum, Black cohosh, Red clover, Piascledine, Avocado plus, Soy, kava, Cimicifuga racemosa rhizome, Licorice red, Trigonella foenum-graecum, Ginseng, fenugreek, Flaxseed, Dong quai, Vitex Agnus-Castus, Evening primrose oil, Yam, Salvia officinalis, alternative treatments, complementary treatments, Phytomedicine, herbal treatments or herbs.

The study inclusion criteria were the randomised controlled trials assessing oral herbal medicin effects on the maturation

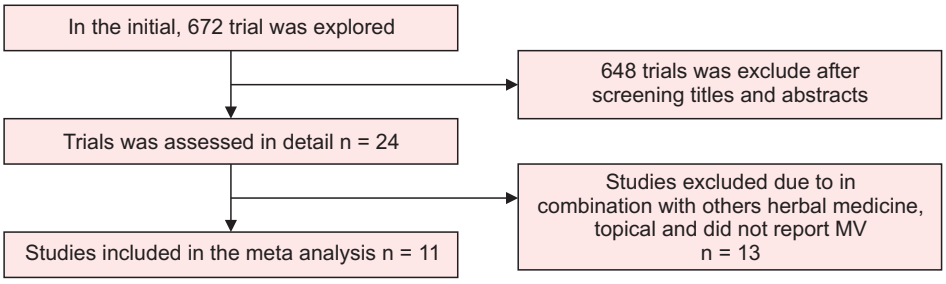

Fig. 1. The process of selection of randomized controlled trials to include in the meta analysis. MV: maturation value.

Table 1. Characteristics of 11 randomized trials included in meta-analysis

References	Duration (months)	Age (years)	Drop out (%)	Type of treatment (No. of participants)	Quality of studies
Baird et al.[13]	1	-	6	Soy foods (n = 63) Regular regimen (n = 24)	8
Murkies et al.[14]	3	54	18	Soy flour supplement (n = 23) Wheat flour (n = 24)	9
Carmignani et al.[15]	4	51	0	Soy supplementation (n = 20) Placebo (n = 20)	11
Chiechi et al.[16]	6	52	43	Soy-rich diet (n = 22) Regular regimen (n = 41)	8
Radhakrishnan et al.[17]	6	53	15	Isoflavone powder (n = 44) Casein protein (n = 41)	10
Knight et al.[18]	3	53	16	An isoflavone supplementation in the form of a powdered drink (n = 9) Isocaloric casein-based beverage (n = 11)	11
Levis et al.[19]	104	52	43	Soy for 1 year (n = 71/81) Soy for 2 years (n = 66/76)	11
Colli et al.[20]	24	53	15	Flaxseed extract (n = 28) Placebo (n = 25)	10
Knight et al.[21]	3	54	4	High dose of Red clover (160 mg) (n = 12) High dose of Red clover (40 mg) (n = 13) Controls (n = 12)	10
Manonai et al.[22]	24	48	17	20, 30, or 50 mg of Pueraria mirifica (n = 52) Placebo (n = 20)	10
D'Anna et al.[23]	7	50-70	0	Isoflavone supplement (n = 198) Regular regimen (n = 193)	12

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value (MV),[11] which is measured following equation:[10]

MV= (% intermediate cells × 0.5) + (% superficial cells)

2. Data extraction and quality assessment

Two reviewers independtly extracted the rerquired data among trials on the databases and the third reviwer was recruited to address the possible disagrements. The data included year of publication, first author, age of participants, rate of drop out, number of patients in the intervention and control groups. According to Physiotherrapy Eviedence Database (PEDro) scale, the two reviwers performed indepently the quality assessment of the trials.

3. Statistical analysis

Comprehensive meta-analysis software[12] was used to determine the standardized mean difference (SMD) for each study. The high heterogeneity among trials made us to reporte the data on the basis of Random Effect Model (Dersimonian and Laird method).

Results

The selection process of randomized controlled trials (RCTs) for enrolling in the current meta-analysis is illustrated in Fig. 1, and the specifications of the studies have been summarized in Table 1. Overall, eleven studies[13~23] met our study inclusion criteria. The SMD of the of MV increased up to 0.48% (95% confidence interval [CI], 0.108–0.871; P = 0.012). The findings revealed high degree of heterogeneity (I^2 = 84%; P < 0.001) (Fig. 2). Therefore, the sensitivity analysis was carried to explore the causes of heterogeneity in crossover trials. The individually exclusion of each study had no significant changes at the level of heterogeneity. No asymmetry was seen in the funnel plot of the trials assessing the effectiveness of herbal medicine on the of MV (Fig. 3). The absence of the publication bias was confirmed using the Egger's regression intercept test (P = 0.056) (Fig. 2). We also

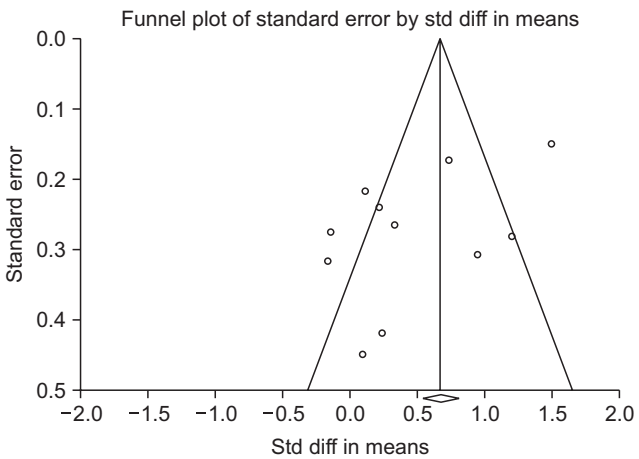
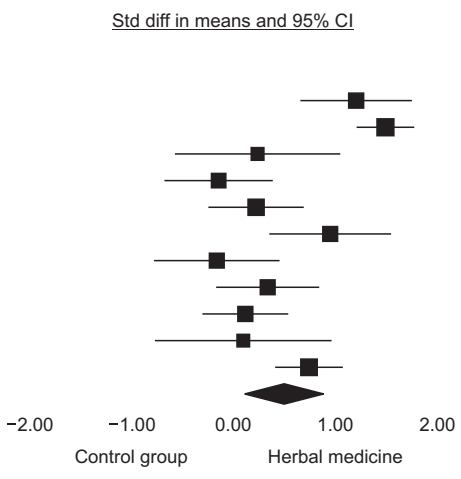


Fig. 3. Funnel plot of publication bias.

Study name	Std diff in means	Standard error	Variance	Lower limit	Upper limit	Z-value	p-value
Manonai Pueraria mirifica	1.205	0.283	0.080	0.651	1.759	4.264	0.000
D'Anna phytoesrogen genisten	1.496	0.150	0.023	1.202	1.791	9.964	0.000
Knight redclover	0.242	0.419	0.176	0.580−	1.063	0.577	0.564
Coli flaxseed	0.141−	0.276	0.076	0.681−	0.399	0.513−	0.608
Baird soy	0.221	0.240	0.058	0.250−	0.693	0.920	0.357
Murkies soy	0.951	0.308	0.095	0.347	1.554	3.088	0.002
Carmignani soy	0.162−	0.317	0.100	0.782−	0.459	0.510−	0.610
Chiechi soy	0.334	0.266	0.071	0.187−	0.856	1.258	0.209
Radhakrishnan soy	0.117	0.217	0.047	0.308−	0.543	0.540	0.589
Knight soy	0.096	0.450	0.202	0.785−	0.978	0.214	0.831
Levis soy	0.737	0.174	0.030	0.396	1.077	4.237	0.000
	0.489	0.195	0.038	0.108	0.871	2.512	0.012



Meta analysis

Fig. 2. Effects of herbal medicine on vaginal epithelial cells (%). Horizontal line: 95% confidence interval (CI), ■: point estimate, ♦: combined overall effect of treatment.

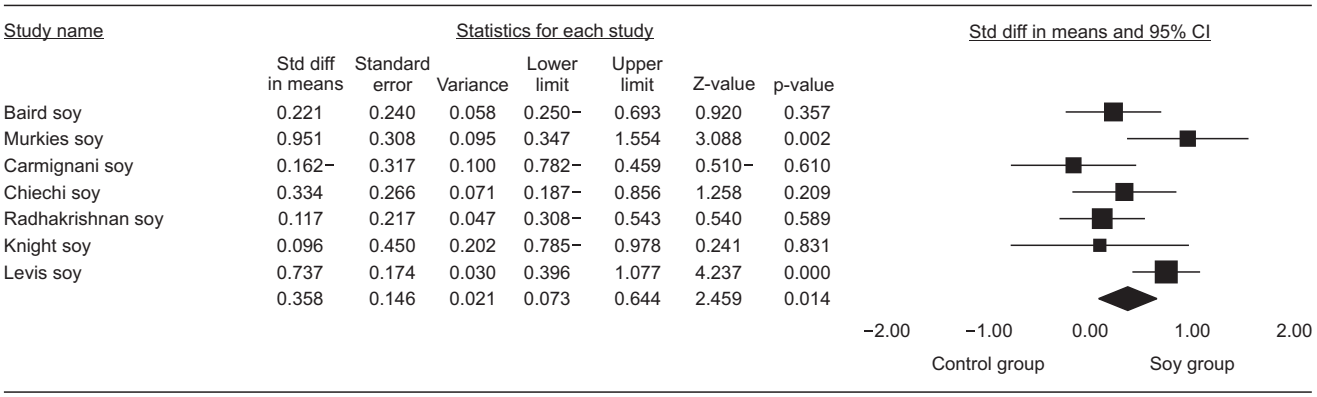


Fig. 4. Effects of soy on vaginal epithelial cells (%). Horizontal line: 95% confidence interval (CI), ■: point estimate, ♦: combined overall effect of treatment.

performed subgroup analysis for the women receiving soy. The of MV showed a significant increase by 0.358% (95% CI, 0.073–0.871; P = 0.014; I^2 = 53%; P = 0.052) (Fig. 4).

Discussion

This is the first meta-analysis to explore the herbal medicine effect on the VECs among menopausal women. According to our findings, the herbal medicine has had statistically significant effect on the vaginal atrophy.

The meta-analysis of several trials demonstrated that the SMD of the MV had significantly borderline increase in the soy group compared to the control group. However, heterogeneity was high. We performed the subgroup analysis in which the meta-analysis was limited to the trials evaluating the effectiveness of the soy on the VECs, which a significant increase was found in the effect size compared to previous meta-analyses. In addition, our meta-analysis had lower (I^2 = 53%) homogeneity compared to the previous investigations (I^2 = 81%).[10]

A systematic review assessed four trials on the effectiveness of administration of topical isoflavones on vaginal atrophy. The topical isoflavones had a beneficial effect on the vaginal atrophy. However, the authors concluded that there is a need to larger RCTs to confirm their results.[24]

In contrast to our meta-analysis that revealed a significant increase in the of MV, a systematic review and meta-analysis recently performed on the effectiveness of phytoestrogen on the of MV among menopausal women showed no significant improvement in phytoestrogen group compared to the control group 0.164% (CI, −0.419 to 0.746).[25]

Several limitations present in this meta-analysis included high heterogeneity, low number of trials, small sample size and methodological flaw, which are better to be addressed in the future studies. The high heterogeneity might be related to the variations and duration of treatment so that some trials did not report pre- and post-treatment means and standard deviations. In addition, no intention-to-treat has been reported in a larger portion of studies contained in the meta-analysis. The quality of trials can be improved due to further trials to follow the CONSORT guidelines.

Conclusion

According to the findings obtained from our meta-analysis, the use of herbal medicines in different studies showed statistically significant positive effects on the VECs. The subgroup analysis of the patients receiving soy indicated also significant effects on the VECs. However, high heterogeneity among the trials makes ambiguous the definitive conclusions on the beneficial effects of herbal on the VECs.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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