

Overview of the Effect of Herbal Medicines and Isoflavones on the Treatment of Cognitive Function

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Objectives: The current overview aimed to present the effect of herbal medicines on cognitive function among menopausal women.

Methods: Two separate authors performed systematic search of the 3 databases of (the MEDLINE Scopus and the Cochrane Central Register Trials) from inception to January 2018. Methodological quality of each study was assessed using the AMSTAR.

Results: According to 2 reviews, soy seems to be effective in enhancing summary cognitive function and visual memory. The effect of isoflavones on cognition was affected by treatment duration as six weeks of treatment improved some dimensions of cognitive parameters, including mental flexibility and planning, and longer treatment period (6 months) improved category digit span test, digit symbol test, and visual scanning test score. The effect of phytoestrogen on cognitive function of menopausal women might be altered age, gender, ethnicity, menopausal status, dosage, and length of treatment, types of cognitive test, location, types of soy, and types of phytoestrogen. Combination of Gingko with ginseng could not improve sustained attention, episode memory, category generation or frontal lobe function. Gingko biloba had no significant effect on planning, memory and sustained attention, except for its limited effect on mental flexibility in late menopause. In addition, other herbal medicines like black cohosh showed no effective beneficial.

Conclusions: Phytoestrogen, soy and isoflavones might have a limited beneficial effect on some aspects of cognition. The phytoestrogens affecting cognition might be modified by age, gender, ethnicity, menopausal status, dosage, and length of treatment, types of cognitive test, location, types of soy, and types of phytoestrogen. (**J Menopausal Med 2018;24:113-118**)

Key Words: Cognition · Herbal medicine · Isoflavones

Introduction

The cognitive ability is gradually and constantly reduced by aging reportedly.¹⁻⁶ A previous study showed that cognitive impairment was less likely in postmenopausal women

with higher estradiol levels.⁷ Nevertheless, 2 longitudinal researches on menopausal transition have failed to find any change in cognitive function in this period, confounding the previous results.^{8,9} In another cross-sectional study on 189 postmenopausal women, the late menopause compared with

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early menopause showed a worsen executive function.¹

There are contradictory results on the effect of hormone replacement therapy (HRT).^{10–13} However, a meta-analysis of 16 studies involving 10,114 women showed that estrogen replacement therapy (estrogens only) or HRT (estrogens combined with a progesterone) had no protective and improving effects on cognitive function.¹⁴ Prolonged HRT led to venous thrombosis, stroke and even increased risk of breast cancer. Consequently, menopausal women has been interesting herbal medicines and dietary supplements like soy, red clover and Ginkgo biloba.¹⁵ There are several systematic reviews assessing the effect of herbal medicines such red clover, Ginkgo biloba, black cohosh and soy.^{15–17} Therefore, it is essential to study simultaneously several reviews to provide existing information for clinicians, policy makers, patients and researchers. The purpose of current overview is to display the effect of herbal medicines on cognitive function among menopausal women.

Materials and Methods

Various kinds of reviews, including systematic review, critical reviews, narrative reviews, rapid reviews, conceptual reviews, and meta-analysis, were assessed to detect the review that evaluated the effect of herbal medicines and soy on cognitive function in postmenopausal women. Two separate authors performed a systematic review search of the 3 da-

tabases of (the MEDLINE Scopus and the Cochrane Central Register Trials) inception up to January 2018. The search terms in English were as follow: (Herbal medicine OR herbal drug OR phytomedicine OR Ginkgo biloba OR phytoestrogen OR soy OR isoflavones) AND (Cognition OR cognitive OR memory) AND (menopause and postmenopause). The manual search of references listed in review, meta-analysis and articles were also carried out to broaden the spectrum of studies. The same authors (the first and second authors) performed search of databases and other sources, assessment of study quality and data extraction (Table 1). A third researcher judged on disagreements prior to final decision. The methodological quality of systematic review was assessed by same authors using the 11-items AMSTAR developed by Oxman et al.¹⁸ (Table 2). Each item was responded by “Yes”, “No”, “Can’t Answer”. A pre-designed form confirmed by research team was used to extract the study data, including type of review, year of publication, first author, study populations, sample size, and main outcomes. Quality of the meta-analysis was assessed s using the 12-items according to CEBMA Center for evidence-based management (Table 3).

Results

Figure 1 shows the process of selecting reviews included into the overview. As can be seen, 2 systematic reviews and

Table 1. Characteristics of 3 studies included in overview

References	Year	Type of review	Age range	Study populations	Type of intervention	Sample size	Conclusion
Clement et al. ¹⁵	2011	Systematic review	46-76	Menopause	Red clover, black cohosh, soy, isoflavones, Ginkgo biloba, a Ginkgo, combination of biloba and Ginseng	414 for isoflavone and 314 for soy	Herbal and soy could not improve cognition
Soni et al. ¹⁷	2014	Review	48-98	Elderly men and women	Phytoestrogens	10,066 women and men	Inconclusive finding of the effect of phytoestrogens on cognition
Cheng et al. ¹⁶	2015	Meta-analysis	52-67	Postmenopause	60-160 mg of soy isoflavone	1,024	Soy showed a beneficial effect on summary cognition functions and visual memory

Table 2. Assessment of methodological quality of systematic using the Assessment of Multiple Systematic Reviews items

References	Year	AMSTAR items										
		1*	2 [†]	3 [‡]	4 [§]	5	6 [¶]	7 ^{**}	8 ^{††}	9 ^{‡‡}	10 ^{§§}	11
Clement et al. ¹⁵	2011	Yes	Yes	Yes	Can not answer	Can not answer	Yes	Yes	Yes	Not applicable	Yes	Yes

*1: Was an 'a priori' design provided?

†2: Was there duplicate study selection and data extraction?

‡3: Was a comprehensive literature search performed?

§4: Was the status of publication (e.g., grey literature) used as an inclusion criterion?

||5: Was a list of studies (included and excluded) provided?

¶6: Were the characteristics of the included studies provided?

**7: Was the scientific quality of the included studies assessed and documented?

††8: Was the scientific quality of the included studies used appropriately in formulating conclusions?

‡‡9: Were the methods used to combine the findings of the studies appropriate?

§§10: Was the likelihood of publication bias assessed?

|||11: Was the conflict of interest stated?

AMSTAR: Assessment of Multiple Systematic Reviews

Table 3. Assessment of methodological quality of systematic according to Center for Evidence-Based Management

References	Year	AMSTAR items											
		1*	2 [†]	3 [‡]	4 [§]	5	6 [¶]	7 ^{**}	8 ^{††}	9 ^{‡‡}	10 ^{§§}	11	12
Cheng et al. ¹⁶	2015	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

*1: Did the study address a clearly focused question?

†2: Was a comprehensive literature search conducted using relevant research databases (e.g., ABI/INFORM, Business Source Premier, PsycINFO, Web of Science, etc.)

‡3: Is the search systematic and reproducible (e.g., were searched information sources listed, were search terms provided)?

§4: Has publication bias been prevented as far as possible (e.g., were attempts made at collecting unpublished data)?

||5: Are the inclusion and exclusion criteria clearly defined (e.g., population, outcomes of interest, study design)?

¶6: Was the methodological quality of each study assessed using predetermined quality criteria?

**7: Are the key features (population, sample size, study design, outcome measures, effect sizes, limitations) of the included studies described?

††8: Has the meta-analysis been conducted correctly?

‡‡9: Were the results similar from study to study?

§§10: Is the effect size practical relevant?

|||11: How precise is the estimate of the effect? Were confidence intervals given?

||||12: Can the results be applied to your organization?

AMSTAR: Assessment of Multiple Systematic Reviews

one meta-analysis were included into the overview in Table 1.

1. The effect of isoflavones on the cognitive functions among menopausal women

One review assessed the effect of isoflavones and soy on cognition. In this systematic review, authors searched seven databases up July 2011 and found 5 studies with 414 menopausal women who examined for the efficacy of isoflavones supplementation on cognition among menopausal women. According to 3 studies, 6 weeks of treatment with

isoflavones could improve some aspects of cognition, such as mental flexibility and planning. There is need for a longer period (6 months) to improve category digit span test, digit symbol test and visual scanning test score. Fourth and fifth study found no effect of isoflavones on memory recall and recognition, working memory, global cognitive function, memory span and executive function. The authors reported that most of studies had a low quality.¹⁵

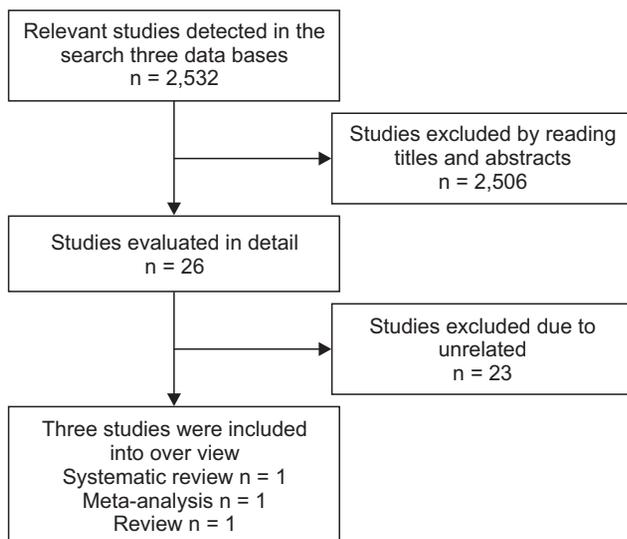


Fig. 1. Search strategy of the study.

2. The effect of phytoestrogens on the cognitive functions in men and women

A review assessed the effect of phytoestrogens on the cognitive function among women and men aged between 48 to 97 years. The result of the review suggested inconclusive findings of the effect of phytoestrogen on the cognitive function. Menopausal women might be affected by variable demographic profiles (age, gender, ethnicity, and menopausal status) and treatment variables (dosage, length of treatment, and type of cognitive test). The length of treatment might influence the results. Good short-term cognitive effect might reverse with treatment continues in elderly. The authors also reported that the type of populations (Asian/European) has impact on the result. European countries with low soy consumption showed no effects of phytoestrogen on cognition. In contrast to Asian countries with higher take of tofu (a non-fermented type) found a negative relation between soy intake and cognitive function, while tempe (fermented soy) had protective effects.¹⁷

3. The effect of soy on cognitive functions in men and women

In a systematic review and meta-analysis evaluating the herbal effect on cognition, the efficacy of soy on cognition was studied within a subgroup of 4 studies on 344 menopausal women. Among these, a good effect on the cognitive function was reported in only one trial, but not in 3 other

studies. Most of studies had low quality.¹⁵

Second study was performed as meta-analysis to assess the effect of soy isoflavones on the cognitive function in the menopausal women. Pooled standardized mean difference (SMD) was significant for summary cognitive function tests (SMD = 0.08; 95% confidence interval [CI] = 0.02–0.15; $P = 0.014$), which showed that the women in soy group received more beneficial effect than that of placebo group. Subgroup analysis was conducted based on the cognitive function domains (visual memory, verbal memory, executive function, attention, and processing speed), the countries (non-US/US), the age (less than 60 years/equal and more than 60 years), the dosage (<90 / ≥90 mg) and the treatment duration (<12 months / 12 months). In the subgroup analysis of the cognitive function domains, the pooled SMD was calculated for the visual memory (SMD = 0.01; 95% CI, 0.02 to 0.18; $P = 0.016$; Heterogeneity, $I^2 = 2%$, $P = 0.426$). Administration of soy isoflavones compared to placebo did not alter significantly other cognitive function domains, including verbal memory (SMD = 0.02; 95% CI, -0.06 to 0.11; $P = 0.606$; Heterogeneity, $I^2 = 37.8%$; $P = 0.075$), executive function (SMD = 0.02; 95% CI, -0.04 to 0.09; $P = 0.522$; Heterogeneity, $I^2 = 18.4%$; $P = 0.239$), attention (SMD = -0.01; 95% CI, -0.08 to 0.06; $P = 0.721$; Heterogeneity, $I^2 = 0%$; $P = 0.593$), processing speed (SMD = 0.03; 95% CI, -0.04 to 0.09; $P = 0.431$; Heterogeneity, $I^2 = 2.7%$; $P = 0.420$) and language (SMD = -0.02; 95% CI, -0.08 to 0.05; $P = 0.586$; Heterogeneity, $I^2 = 0%$; $P = 0.464$). The results of subgroup analysis showed that the SMD was not affected by age, dosage and length. The result of subgroup analysis for non-US countries was significant (SMD = 0.12; 95% CI, 0.00 to 0.25; $P = 0.044$; Heterogeneity, $I^2 = 70.9%$; $P = 0.008$). In fact, studies showing good effect of soy on the cognitive function have mainly been performed in non-US countries.¹⁶

4. The effect of red clover on the cognitive functions

The second study, a systematic review assessed the efficacy of phytoestrogens such as red clover, Ginkgo biloba, isoflavones and other herbal medicines such as black cohosh on the cognitive function. Two studies evaluated the efficacy of red clover cognition among 61 menopausal women. According to the result of systematic review, the red clover

showed no positive effect on the processing speed, memory, verbal ability, frontal cortex function compared to placebo in the menopausal women.¹⁵

5. The effect of Gingko and ginseng on the cognitive functions

Two studies included into systematic review assessed the effect of Gingko and ginseng on the cognition.

The first study evaluated the combination of Gingko with ginseng on the cognition and showed that this combination could not improve sustained attention, episode memory, category generation, or frontal lobe function in 6-week follow up. In another 6-week study, the effect of Gingko biloba on the cognitive function was assessed in the menopausal women. The subgroup analysis was performed based on the menopausal status: early stage (early menopause, equal to and less than 5 years after menopause) and late stage (more than 5 years after menopause). The Gingko biloba had no significant effect on planning, memory and sustained attention except for its limited effect on mental flexibility in late menopause.¹⁵

6. The effect of black cohosh on the cognitive functions

Based on one study, the black cohosh did not improve verbal memory and California verbal learning test.¹⁵

Discussion

In the current study, 3 systematic reviews in the overview studied the efficacy of herbal medicines, including soy, red clover, ginkgo biloba, combination of ginkgo biloba with ginseng on some aspects of memory and cognitive function.

Several mechanisms of action have been commonly found in the phytoestrogens and estrogen, boosting cognitive function, such as increased choline acetyltransferase and brain-derived neurotrophic factor in the hippocampus and frontal cortex.¹⁹ In line with these mechanisms of action, phytoestrogen, soy and isoflavones may have a limited beneficial effect on some aspects of cognition.

The red clover and combination of Gingko with ginseng had no positive effect on the cognition. The Gingko biloba

had limited effect on the mental flexibility in late menopause. Moreover, other herbal medicines like black cohosh indicated no beneficial effect. According to 2 reviews, the soy seems to be effective in increasing the summery cognitive function and visual memory. The effect of phytoestrogen on the cognitive function of menopausal women may be modified by age, gender, ethnicity, menopausal status, dosage, length of treatment and types of cognitive test, location, types of soy and types of phytoestrogen. The effect of isoflavones on the cognition was affected by duration of treatment, as six weeks of treatment improved some aspects of the cognition such as mental flexibility and planning and longer period of treatment (6 months) improved category digit span test, digit symbol test, and visual scanning test score.

The result of current overview should be interpreted with cautions because almost all of included studies in systematic review and meta-analysis included in overview had a major methodological difficulty. Most of studies did not report or explained clearly randomization technique, rate of dropouts, attrition rate, no use of intention to treat, blinding method, sequence generation, and method of determining sample size. It is highly recommended that future studies should be designed and reported according to the consort criteria to provide high quality studies for improving the quality of systematic review and meta-analysis. Adequate sample size would be considered in future trials to perform specified subgroup by menopausal status, dosage, length, age, gender, and ethnicity.

Conclusion

Phytoestrogen, soy and isoflavones may have a limited beneficial effect on some aspects of cognition. The effect of phytoestrogens on the cognitive function may be altered by age, gender, ethnicity, menopausal status, dosage, length of treatment and types of cognitive test, location, types of soy, and types of phytoestrogen.

Conflict of Interest

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

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