Effects of phytoestrogens in the treatment of postmenopausal depressive disorders: A systematic review and meta-analysis

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Abstract

Background:Menopause-related symptoms are now a major public health concern and depression is one of the most common and specific symptoms of post-menopause. Objectives: The purpose of this study was to assess the effectiveness of different kinds of phytoestrogens in the remission of depression for postmenopausal women. Methods: A comprehensive search for relevant studies published between January 1, 1951 and June 30, 2020 was conducted in PubMed, the Cochrane Library, Chinese Biomedical Literature Database, Web of Science and EMBASE. Endnote X9 was used for screening articles, the Stata12.0 and Review Manager 5.3 for analyzing data. Results: Phytoestrogens had a have a significant positive effect on depressive symptoms for climacteric women compared to the placebo (SMD=-0.51; 95% [CI]=-0.74 to -0.29; I2=72.4%; P<0.05). The effectiveness in isoflavones (SMD=-0.64; 95% [CI]=-0.97 to -0.32; I2=56.2%, P>0.05) is slightly better than non-isoflavones (SMD=-0.5; 95%[CI]=-93 to -0.07; I2=72.8%, P<0.05). The total intake of phytoestrogens in the high dose group was the most effective in alleviating the symptoms of postmenopausal depression (SMD=-0.69; 95%CI=-1.09 to -0.35, P<0.05). Postmenopausal women in Europe had the best improvement in efficacy after taking phytoestrogens (SMD=-0.72, 95% CI=-1.09 to -0.35, I2=65.5%, P<0.05). Conclusions: Our study demonstrated that phytoestrogen significantly reduce depression among postmenopausal women, with more effect for larger dosages. Phytoestrogen should be considered as a safe and effective complementary medicine for postmenopausal symptoms in place of estrogens.

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Conclusions: Our study demonstrated that phytoestrogen significantly reduce depression among post-menopausal women, with more effect for larger dosages. Phytoestrogen should be considered as a safe and effective complementary medicine for postmenopausal symptoms in place of estrogens.

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KEYWORDS: Post-menopausal women; Phytoestrogens; Depression; Isoflavones;

1.Introduction

Menopause is considered as the end of woman's reproductive life, generally defined as "cessation" of menstrual periods for twelve consecutive months[1]. Both health needs and risk factors are likely to change as women pass through menopause[2]. Menopause-related conditions are now a major public health concern[3]. The most common and specific symptoms of menopause include flushing, sudden sweating and chills, palpitations, feeling pressure in the head and chest, difficulty concentrating, and depression[4-6]. Depression is a common psychiatric disorder that can lead to disability and death[7,8], causing substantial personal, family, social, and economic burdens[9]. Accumulating evidence suggests that estrogen could plays a role in treating depression and is a method of relieving symptoms of menopause[10] but has great side effects and risks, such as stroke, thromboembolism events, breast cancer, and vascular diseases[11].However, in the meanwhile, Morrison et.al said that hormone replacement therapy (HRT) could not treat the post-menopause including relieve depressive symptoms in them[12]. Nowadays, have proposed phytoestrogens - compounds extracted from plants, primarily isoflavones that mimic or modulate endogenous estrogens[13] – as an alternative approach to treating post-menopause depression, without the risks associated with estrogens[14].Many women now choose treatments associated with herbal medicine rather than exposing themselves to the risks associated with hormone replacement therapy, with a greater focus on maintaining their physical and cognitive health[3,15].

Therefore, given the increasing attention of post-menopause women and their immediate and long-term impacts on the health of the population[16], the interest in studying the anxiety and depression has increased[17], mainly due to cultural changes in their expectations regarding their abilities to continue working and caring for family members[18]. However, no definitive conclusions regarding the effects of phytoestrogens on menopausal depression were available until now[19]. Some researchers' findings indicated a significant improvement[20,21], while some studies concluded that the treatment of soy isoflavones did not produce a reduction for depressive[22].

Perimenopausal women are more vulnerable to depression than postmenopausal women. There is much research on perimenopausal women[23], but relatively less research on how to alleviate depression in post-menopausal women. So our study was aims to systematically review and synthesize scientific evidence to conduct a meta-analysis of randomized controlled trials (RCTs) to investigate the effects of phytoestrogens in alleviating depressive symptoms in post-menopause, in order to contribute to the development of future research and the development of public health[1].

2.Method

The Cochrane Handbook for Systematic Reviews of Interventions and PRISMA Statement was used to guide the conduct and reporting of this review[24]. A literature search was done using four electronic databases.

2.1. Data sources and search strategy

A comprehensive search for relevant studies published in English or Chinese between January1, 1951 and June 30,2020 was conducted in databases such as PubMed, the Cochrane Library, Chinese Biomedical Literature Database, Web of Science and EMBASE. The search key words included (depression OR Depress* OR blue* OR melancho*) AND ("Plant Estrogens" OR "Phyto-Estrogen" OR "Estrogen-Like Plant Extracts") AND (climacteric* OR menopause* OR "climacteric period" OR involutional)]. Details on the search strategy are

provided in the Supplemental Material Table.1. Moreover, the reference lists of the studies were searched manually to identify additional studies not indexed in databases[25]

Reference lists of identified trials and review articles were manually scanned to identify any other relevant studies. The Clinical Trials.gov website was also searched for randomized trials that were registered as completed but not yet published[26].

2.2. Selection criteria and Data extraction

Inclusion criteria were as follows: (1) age from 45 to 70 years, with at least 12 months of menopause at baseline, were in good general health, had not a menstrual period in the preceding year or had undergone surgically induced menopause (2) the presence of vasomotor and depression symptoms clinically detectable; follicle-stimulating hormone (FSH) plasma levels greater than or equal to 25 IU/L (3)women experiencing menopausal symptoms without any hormone therapy (4) intervention with an oral phytoestrogen (5) the study was an RCT.

Studies were excluded for the following reasons:(1)reported previous or current use of hormone therapy, history of ovariectomy or hysterectomy, or no menopausal symptoms (2) history of diabetes or hypertension, history of thromboembolism, severe endometriosis, epilepsy, asthma, hyperprolactinemia, first degree relative having a history of breast cancer (3)the study researched mental illness without depression (4) numerical outcome data were not provided. The degree of mood disorders was not considered among the inclusion or exclusion criteria.

Articles identified in the databases were screened by two reviewers (J.L. and H.J) independently with a standardized approach on June 30, 2020, the title or abstract of all publications that were close to the outcome were reviewed for eligibility and met to identify and resolve the differences between each other[27].

All completed randomized controlled trials assessing the effects of phytoestrogens compared with placebo, and that reported one or more of the primary or secondary outcomes, were eligible for inclusion.

Eligible studies were read in their entirety, and the information was recorded in an Excel spreadsheet.

2.3. Risk of Bias Assessment

Risk of bias of each individual study was evaluated by two reviewers[26]. To assess the quality of RCTs, we used the assessment tool for "risk of bias" from the Cochrane Handbook version 5.1.0[27]. Studies were judged based on criteria to evaluate random sequence generation, allocation concealment, blinding of participants/personnel and outcome assessment, incomplete outcome data and selective reporting. RCTs considered to be at low risk of bias, if allocation concealment, blinding of participants and outcome assessors were all coded "low" and the number of dropouts and reasons for dropout were reported. Otherwise, the RCTs considered to be at high risk of bias[26]. If the risk of bias couldn't be determined in any of the segments (e.g. information not provided) the risk of bias was classified as unclear.

2.4. Data synthesis and statistical analysis

Data were further analyzed by using Stata 12.0 and Review Manager 5.3. To estimate effect sizes for continuous outcomes, we computed standardized mean differences (SMD) with 95% confidence intervals(95%CI)[27]. Furthermore, post-intervention depressive outcomes were pooled using a random-effects model, for this model generates a more reliable estimate than the fixed effect analysis; especially when there is substantial heterogeneity[29].

The primary outcome measurement of efficacy was the change score in depressive symptoms after using different kinds of phytoestrogen, according to the criteria used in each trial. We allowed for heterogeneity in treatment effects between studies, the extent of heterogeneity interpreted by the total percentage of variation between the studies concerned, measured with the I^2statistic classified as low (I^2[?]25%), moderate (I^2>25% and <75%), or high (I^2[?]75%)[30]. Additionally, the Q-statistic was used to assess the presence of

heterogeneity. PQ statistic[?]0.05 was considered to indicate no significant heterogeneity among the included studies[31].

To assess the influence of each individual study, leave-one-out sensitivity analysis was performed iteratively by removing one study at a time to confirm that the findings were not influenced by any single study. Publication bias was assessed by visually inspection of funnel plots and using the Begg's test[32]. Begg's test was interpreted by the *P*value, the *P* value less than 0.05 indicates publication bias[26].

In order to compare the effects of various kinds and doses of phytoestrogens more intuitively, we calculated the total amounts (days × daily doses = total amount). After sorting by the total amount of phytoestrogens intake, we defined 9 grams as median dose. The amounts more than 0 and less than 9g were classified in the low-dose group(Low Dose: 0<dose<9); the dose more or equal to 9g and less than 18g were in moderate group (Moderate Dose: 9[?]dose<18); more or equal to 18g were in the high dose group (High Dose: dose[?]18).

3.Result

3.1. Selection and Characteristics of Studies

Overall, 2,183 studies were identified, and 54 met the inclusion criteria and were considered relevant. Only ten studies reported the data to be included in the meta-analysis, involving a total of 1,248 individuals with intervention periods varying from six weeks to two years[14,20,22,33-39].

Characteristics of studies were shown in Table 1. Included studies were published in four continents of eight countries: Japan, Korea, India, Brazil, Canada, Austria, Australia, and Italy between 2002 and 2017. Furthermore, six scales were used to evaluate the depression index before and after treatment: the center for epidemiological studies depression scale (CED-S)[7], the Hamilton depression rating scale (HADS)[40], the Zung's self-rating depression scale(SDS)[41], the profile of mood states (POMS)[42], the Greene climacteric scale (GSC)[43] and the Kupperman menopause index (KMI)[44]. The different types of phytoestrogens were used following in included studies: Kava-Kava(extract of Piper Methysticum)[39],red clover isoflavones[20,38], daidzein isoflavone[33] , soy isoflavones[22] , phytoestrogen genistein[14], isoflavones aglycone[34] , fenugreek extract[36] , Schisandra chinensis[35] and resveratrol[37]. Of them, five studies employed isoflavones including red clover isoflavones, daidzein isoflavone, soy isoflavones and isoflavones aglycone. Four studies analyze treatments in the low-dose group, five in the moderate dose group, and four in the high-dose group. The maximum total amount was 86.5g[36], while the minimum one was only 1.5g[34].

3.2. Outcome Measures of Meta-Analyses

3.2.1. Primary Outcome Analyses

The results of pooled analyses show that phytoestrogens have a positive effect compared to placebo on depressive symptoms for climacteric women (SMD=-0.51; 95% [CI]=-0.74 to -0.29;I^2=72.4%; P <0.05) (Fig.2). In Shamshad et al[36] , intake of 1000mg/day of fenugreek phytoestrogens extrated for 3 months got the most significant change in outcome (SMD=-1.12; 95% [CI]=-1.62 to -0.61) , Lipovac et al[20] conducted a double-blind, randomized, crossover study (with a wash-out period of one week) on two groups (red clover and placebo) for 12 weeks was the second largest effect (SMD=-1.05; 95% [CI]=-1.62 to -0.61). While using the same dose of red clover isoflavones, Jeffrey et al [38] report the smallest effect with no significant improvement in subscale of GCS's 'depression' item either in Promensil (SMD=-0.08; 95%[CI]=-0.38 to 0.23)or Rimostil (SMD=-0.18; 95%[CI]=-0.48 to 0.13) groups compared to the placebo group.

3.2.2. Subgroups Analyses

The first subgroup analyses based on different types of phytoestrogens in all assess scales showed (Fig.3)that the effectiveness of menopausal women in non-isoflavones(SMD=-0.57; 95% [CI]=- 0.92 to 0.23;I^2*=67.4%, P<0.05*) is slightly better than isoflavones (SMD=-0.47; 95% [CI]=-0.77 to 0.17;I^2*=72.5%, P<0.05*), though these differences are not significant. However, when we excluded the index of GCS and KMI(Fig.4), we find that the changed data in isoflavones(SMD=-0.64; 95% [CI]=-0.97 to -0.32;I^2*=56.2%, P>0.05*) is better than non-isoflavones (SMD=-0.5; 95% [CI]=-0.93 to -0.07;I^2*=72.8%, P<0.05*).

The second subgroup analyses were based on different assessed scales. Since in this case the outcome measure is the same within each use of studies we use WMD. The study of Lipovac et al[20](Fig.5) showed that using the SDS as assessed scale's changed data is the most (WMD=-7.2; 95% [CI]=-9.76 to -4.64). Meanwhile, the data in GCS (WMD=-0.47; 95%[CI]=-1.01 to 0.07; I^2=*75.7%*) and KMI (WMD=-1.22; 95% [CI]=-4.21 to -1.77) almost have no change.

The third subgroup analyses were based on different dosages, which showed that the total intake of phytoestrogens in the high dose group was the most effective in improving the symptoms of menopausal depression (SMD =-0.69; 95% CI = -1.10 to -0.28;I^2=71.3%) (Fig.6), while compared with the low (SMD =-0.22; 95% CI = -0.42 to -0.01;I^2=11%;P >0.05) and moderate dose groups, the effectiveness in low dose group was not significant (SMD=-0.58; 95%CI=-0.93 to -0.23;I^2=62.9%, P <0.05).

Due to the fact that the included studies were published in four continents of eight countries, in the fourth subgroup we found that the menopausal women in Europe had the best depressive remission (SMD=-0.72, 95% CI=-1.09 to -0.35I^2=65.5%,P <0.05),while the women in Oceania relieved the least (SMD=-0.29;95% [CI]=-0.73 to -0.16)(Fig.7). The effect is significant in every region.

3.3. Sensitivity and Risk of Bias

In sensitivity analysis, there were no particularly prominent sensitivity issues in the included literature (Supplementary Material Fig 1). Begg's test did not show a statistical difference so there is no indication of publication bias (P =0.502).

Risk of bias assessment was shown in Supplemental Material Fig 2-3 Participants were selected and both baseline and follow-up conditions were well described. All studies were based on validated tools used to assess depressive symptoms. Baseline characteristics were not significantly different between control and intervention groups. Random sequence generation was deemed adequate in five of ten trials[14,20,36-38]. Blinding of outcome assessment was unknown in five trials[22,33,34,38,39]. One trial[34] was assessed as high risk of bias in selective outcome, on account of the fact that the pre-specified primary outcomes had not been reported. Three [34,37,38]of the studies reported conflicts of interest.

3.4. Adverse Events

In Table 2, five of the 10 studies assessed adverse effects (AEs)[22,33,35,38,39,45], reporting abdominal pain, nausea, headache, constipation, diarrhea, epigastric, flatulence increased in appetite, pain breast, tremor of extremities, blurred vision, insomnia, cold or upper respiratory tract, generalized rash, infection, myalgia, arthralgia as AEs that occurred intervention groups.

The study by Ishiwata et al.[33] reported in one case, the subject developed a generalized rash in the second week of intervention. In Jeffrey et al.[38], Park et al.[35] and Rilva et al.[22] reported total 20 cases in abdominal pain, which is the most common adverse reaction. Furthermore, there were two patients who reported constipation[22], seven reported diarrhea[22,38], one reported upper abdominal symptoms and two reported stomach flatulence of other gastrointestinal symptoms. In Cagnacci et al.[39] and Jeffrey et al.[38], five women experienced nausea.

4. Discussion

4.1. Main findings

Overall, ten studies were included, involving a total of 1,248 individuals by means of different interventions, different assessed scales and different doses on four different continents.

Our systematic review and meta-analysis could provide suggestive evidence of the superiority of phytoestrogens over placebo treatments. The quality of evidence in this study was low or moderate because of several unclear and high risk of bias. Additionally, the total number of RCTs and the sample size included in our analysis was not sufficient to draw firm conclusions.

4.2. Interpretation of findings

Overall, phytoestrogens have a positive significant effect in reducing depression for post-menopausal women, with stronger effects for larger dosages. However, there are some nuances.

The forest diagram of the main outcome showed that the effects of different kinds of phytoestrogens are different. The first subgroup analysis compares the isoflavone group and the non-isoflavone group. The results showed that the effect of the non-isoflavone group was better than the isoflavone group, but both of them showed moderate heterogeneity. In order to reduce the heterogeneity, assessment scales of climacteric evaluation (GCS and KMI) with depression items was excluded for supplementary analysis. It was found that the result of isoflavone group was higher than that of non-isoflavone group. A noteworthy finding is that heterogeneityI^2 value of the isoflavone group decreased from 72.5% to 56.2%, but the heterogeneity of the non-isoflavone group increased from 67.4% to 72.8%, $p < 0.05$. Through this finding, we suspected using different evaluation scales may have a heterogeneity reason with the results. Therefore, we carried out the second subgroup analysis, and found that the use of menopause scale GCS[43] and KMI[44] which with depression items had the least significant improvement effect on climacteric women after intaking phytoestrogens. Considering that KMI and GCS are the comprehensive and validated tools for assessing menopausal symptoms, the scores may be influenced by the presence of somatic symptoms related to climacteric. Hence, we hope that the specific depression scale can be unified in the evaluation methods in the future clinical research.

The third subgroup was based on the effects of different doses associated with the main outcome. Although both Lipovac et al.[20]and Jeffrey et al.[38] used the same isoflavones as intervention, the difference of the two was a large variation. Using different evaluation scales and different total dose intake, were two reasons may affect this result. Among them, the total dose in the Shamshad et al.[36] was the most, 86.5g in 90 days, and the effectiveness was most (SMD=-1.12 95% CI=-1.62 to -0.61). The total dose in Jeffrey et al.[38] the was the second least, 57mg in 90 days, and the effectiveness was least (SMD=-0.08 95% CI=-0.38 to 0.23). In addition to the use of GCS as an evaluation scale, which may cause a heterogeneity, it also indicated that the effect of fenugreek may not be such useful. Furthermore, the result may mean the proper higher dose, may have the better effect, but more clinical studies are still needed to further standardize the duration and dosage of phytoestrogens. Beyond that, the mean BMI value of this trial was the highest among all studies included, so we suspected that the weight differences may also be a reason for climacteric women in depressive disorder[46]. However, we could only make a conjecture, because the original data of each subject could not be obtained.

The fourth subgroup was based on the four continents of eight countries. The forest diagram showed that the depression of menopausal women had a relative better improvement after treatments by phytoestrogens in Europe, but slightly in Asia and the Oceania. As the dietary habits of the women in the countries studied are very different, it is possible that the use of soy products in Japan and Korea may affect the results of the phytoestrogens. And considering ethnic diversity in different regions, more experiments are needed to explore the specific conclusions.

In the analysis of the four various subgroups, the heterogeneity ranged from 0% to 87.1%. The high heterogeneity of the studies, mainly regarding the scales use and doses of phytoestrogens, underlines the necessity of further clinical trials and assesses the effectiveness of phytoestrogens on the long term in the future.

4.3. Biological Mechanisms and Plausibility

A study has been found of the mechanism of phytoestrogen action in Lephart et al.[47], which investigated the levels of brain Bcl-2-associated death protein (a proapoptotic member of Bcl-2 protein family) and neuron-specific β-III tubulin (an early marker of neuronal differentiation/survival) in rats, suggesting that soy isoflavones can potentially ameliorate anxiety, and quicken recovery from trauma. Also, phytoestrogens such as quercetin, trans-resveratrol and equol have been shown to have antidepressant-like effects in rodents[47].

Therefore, based on animal trials[48], the effectiveness of phytoestrogens has scientifically been proved and they can be used to manage stress and stress-related diseases.

4.4. Strengths and limitations

This is the first systematic review and meta-analysis of the effects of phytoestrogens on depression in post-menopausal women, including 1,248 menopausal women. Combined with the four subgroups analysis, we explored the effect of different phytoestrogens on menopausal women's depression comprehensively and detailed adverse reactions after intake.

However, there are several limitations that need to be mentioned. Due to the fact that the types of phytoestrogens and their dosages were in differences and weakness of methodologies in the included studies (such as inadequate treatment allocation, small sample size and unclear blinding method), Given the low quality of much of the current evidence, more well-designed studies are needed to further elucidate the associations, and more normative studies are needed to draw conclusions.

4.5. Conclusion

Menopausal discomfort caused by hormonal imbalances is common in middle-aged women. In conclusion, our study showed a favorable effect of phytoestrogens for the management of depression in menopausal women. However, there still need more clinical trials on different phytoestrogens, in order to unify the most appropriate dosage, duration and other treatment applications to relieving the menopausal depression as much as possible.

Contributors

LJY and YPJ designed the study.

LJY and LHJ did the literature searches and designed the data extraction form.

LJW and LHJ extracted data.

LJY and LJW cross-checked the data extraction.

LJY did the statistical analyses.

QJ and HJN supervised the statistical analyses.

All authors wrote the paper, read, and approved the submitted version.

Conflict of interest

The authors declare that they have no conflict of interest.

Provenance and peer review

This article has undergone peer review.

Ethical statement

The study did not warrant institutional review board approval as no human subjects were involved.

Fig.1. Flow diagram;

Fig.2 Association between various phytoestrogens with the effectiveness of depression.

Fig.3 The Subgroup1.1: Association between isoflavone and non-isoflavone groups with the effectiveness of menopausal women to remission depression in different evaluation scales

Fig.4 The Subgroup1.2: Association between isoflavone and non-isoflavone groups with the effectiveness of menopausal women to remission depression in different evaluation scales except KMI and GCS scales.

Fig.5 The Subgroup2: Association between various scales with the effectiveness of menopausal women to remission depression.

Fig.6 The Subgroup3: Association between three total intake doses' group with the effectiveness of menopausal women to remission depression.

Fig.7 The Subgroup4: Association between eight countries of four continents with the effectiveness of menopausal women to remission depression.

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Table 1 Characteristic of the studies included in the meta-analysis

References	Country	Design	Age(years)	BMI	Duration(Day)	Type of interv
			Mean(SD)	Mean(SD)		
Cagnacci 2002 P:34	**Italy**	**RCT**	**50.73(0.79)**	**26.39(3.52)**	**90**	**Kava-Kava(ex**
Jeffrey 2003	**Canada**	**RCT**	**52.3(3.71)**	**26.14(4.94)**	**90**	**Red clover iso**

References	Country	Design	Age(years)	BMI	Duration(Day)	Type of interv
P:85	GCS					
Ishiwata 2009	Japan	RCT	50.53(4.78)	22(3)	90	Daidzein isofla
P:33	POMS					
Rilva 2009	Brazil	RCT	53.2(5.7)	/	120	Soy isoflavones
P:37	CES-D					
Lipovac 2010	Austria	RCT	53.5(7.1)	24.7(3.9)	180	Red clover iso
P:59	HADS, SDS					
Atteritano 2014	Italy	RCT	52.5(2)	24.31(4.85)	365/730	Phytoestrogen
P:123	SDS					
Hirose 2015	Japan	RCT	48.7(5.18)	22.03(3.06)	60	Isoflavones agl
P:29	HADS					
Shamshad 2016	India	RCT	53.31(4.32)	26.92(4.09)	90	Fenugreek ext
1000mg/day (12weeks)	86.5	placebo	I:38			
P:32	GCS					
Park 2016	Korea	RCT	52.28(5.26)	23.09(3.28)	42	Schisandra chi
P:18	KMI					
Evans 2017	Australia	RCT	61.5(1.1)	26.7(0.8)	98	Resveratrol
P:41	CES-D, POMS					

SDS, the Zung's Self-Rating Depression Scale; GCS, the Greene Climacteric Scale; POMS, the Profile of Mood States; CES-D, the Center for Epidemiological Studies Depression Scale; HADS, the Hospital Anxiety and Depression Scale; KMI, Kupperman Menopause Index; QOL, Quality of Life; SD=Standard-deviation

Table2 The adverse events in all included studies.

Parameter	Parameter	Kava-Kava	Kava-
		100 mg/day	200mg
Gastrointestinal symptoms			
Abdominal pain	Abdominal pain	2	2
Nausea	Nausea	1	1
Constipation	Constipation	-	-
Diarrhea	Diarrhea	-	-
Epigastric	Epigastric	-	-
Flatulence	Flatulence	-	-
Other Events	Other Events		
Increase in appetite	Increase in appetite	-	-
Pain breast	Pain breast	-	-
Tremor of extremities	Tremor of extremities	-	-
Dizziness	Dizziness	-	-
Blurred vision	Blurred vision	-	-
Insomnia	Insomnia	-	-
Cold or Upper respiratory tract infection	Cold or Upper respiratory tract infection	-	-
Headache	Headache	-	-
Myalgia	Myalgia	-	-
Arthralgia	Arthralgia	-	-
Generalized Rash	Generalized Rash	-	-
Total	Total	3	3

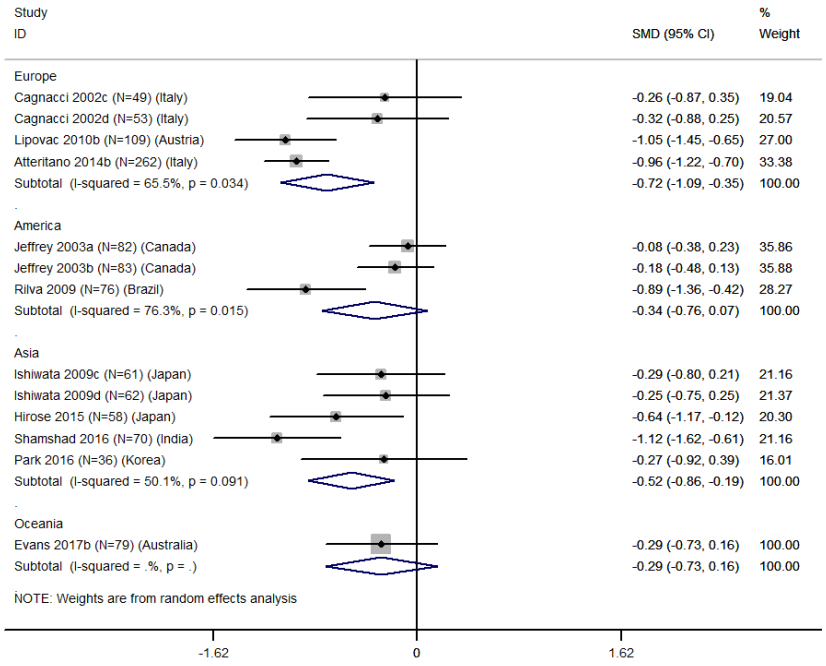

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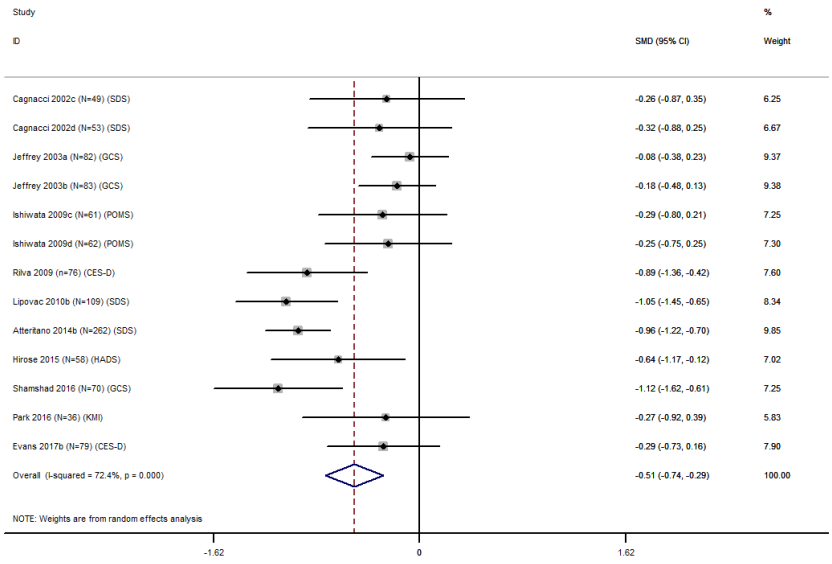
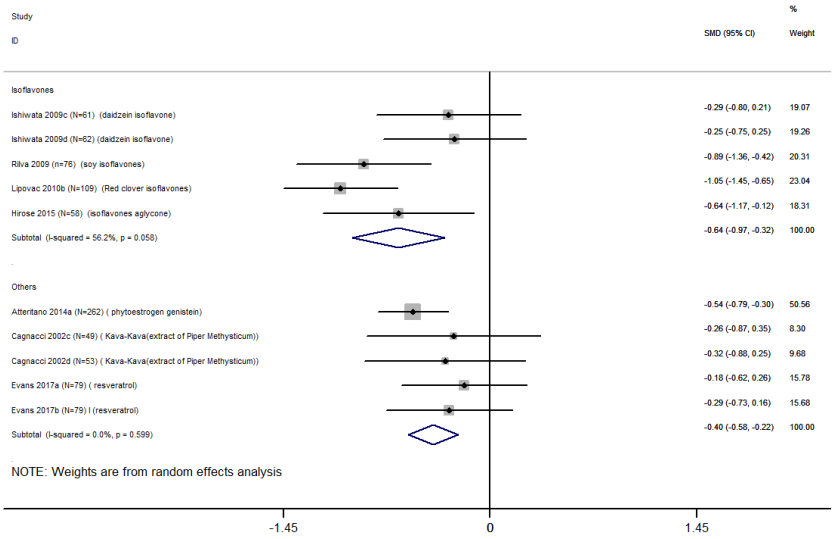
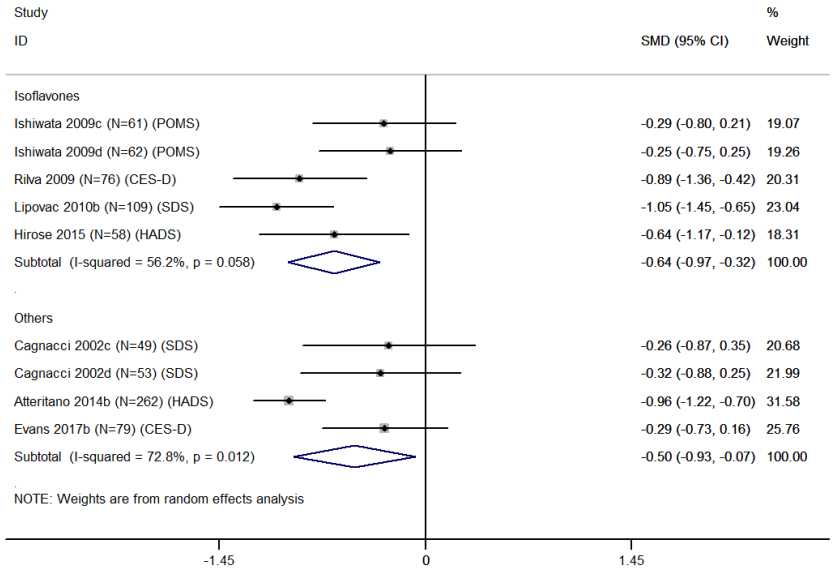
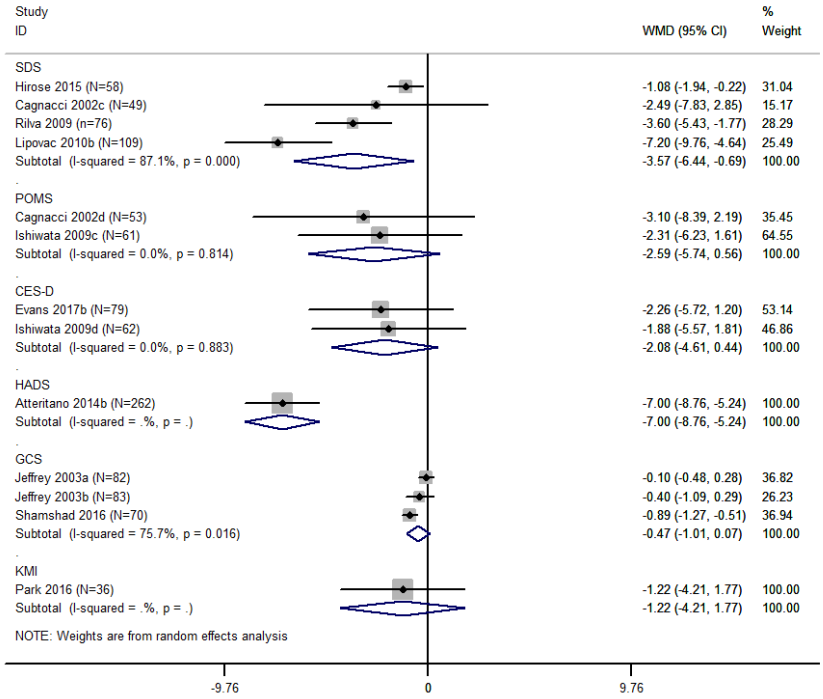
Fig.1. Flow diagram.doc available at https://authorea.com/users/344317/articles/470895-effects-of-phytoestrogens-in-the-treatment-of-postmenopausal-depressive-disorders-a-systematic-review-and-meta-analysis









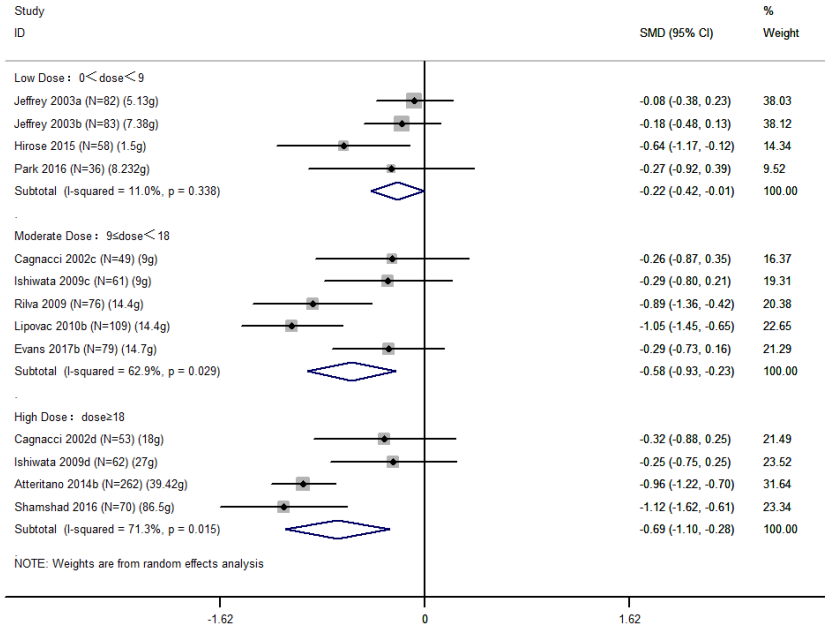


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Table S1.docx available at https://authorea.com/users/344317/articles/470895-effects-of-phytoestrogens-in-the-treatment-of-postmenopausal-depressive-disorders-a-systematic-review-and-meta-analysis