

Effect of Isoflavones on Hot Flushes Women Menopause: A Systematic Review

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Abstract: Aim: Reviewing the effects of soy isoflavones and red clover isoflavones on the incidence of hot flushes in menopausal women. Method: search articles via database: Proquest, Scopus, and ScienceDirect, Limits of 2007-2017 there are 13 RCT research journals. Results: Of the 13 journals of 10 journals using soy isoflavones intervention, 2 journals used red clover intervention and 1 journal using intervention combinations of soy isoflavones and red clover. Soya isoflavones intervention of 50.7 mg, 90 mg, 80 mg, 100 mg, 70.56 mg, 60 mg, 80 mg, 30 mg genistein and red clover isoflavones as much as 80 mg showed a decrease in the incidence of hot flushes. Soy isoflavones intervention of 35 mg, 70 mg and red clover isoflavones of 37.1 mg / d did not show a decrease in the incidence of hot flushes. Combination interventions of 60.8 mg soy isoflavones and 19.2 mg red clover showed a decrease in the incidence of hot flushes. Conclusion: soy isoflavones and red clover isoflavones have a positive effect on reducing the incidence of hot flushes in postmenopausal women but a similar study is required with larger numbers of samples and corresponding measuring instruments.

1 INTRODUCTION

Menopause is characterized as decreased levels of estrogen and progesterone which can lead to the development of some symptoms such as hot flushes, night sweats, vaginal dryness, mood disorders, decreased libido, insomnia, lethargy or fatigue, irritability, anxiety, depression, heart palpitations and pain (Borrelli and Ernst, 2010). Hot flushes usually occur for at least 1 year to 5 years after menstruation ends permanently. Hot flushes in menopausal women is a vasomotor response of reduced estrogen, a symptom that generally affects the quality of life of women and makes women seek to perform effective and safe treatments. Epidemiological data indicate the highest prevalence of hot flushes of 60% are at the age of 52-54 years (Ferrari, 2009). Hot flushes incidence of 18% in China, 15% in Japan, and 14% in Singapore. While in Europe and America, hot flushes incidence could reach 80-85% and in Brazilian women reach 70% (Thomas *et al.*, 2014).

Decreased estrogen levels are a major factor in loss of bone density, vaginal epithelial atrophy, hot flushes and mood changes. A number of women do the prevention of menopause symptoms by using

hormone replacement therapy. Research on the effects of hormone replacement therapy by the Women's Health Initiative Study (WHI) mentions an increased risk of breast cancer and cardiac complications early in its use. Thus, many women switch by using complementary and alternative therapies (Levis *et al.*, 2010)

Some women use complementary and alternative therapies to treat menopausal symptoms by using soy products, herbs and other alternative complementary therapies. The main reason for the use of complementary and alternative therapies is the fear of the effects or risks of long-term use of hormone replacement therapy (hormone replacement therapy). In fact, complementary and alternative therapies are safer than hormone replacement therapy (Posadzki *et al.*, 2013). The derivative of estrogen is phytoestrogen with 3 classification of isoflavones, lignans and coumestans. Isoflavones were found to have high concentrations in soybeans, soy products (such as tofu) and red clover (Borrelli and Ernst, 2010).

In the study of Toku *et al.* All found that soy isoflavones given for 6 weeks to 12 months can reduce the incidence of hot flushes by almost 21%. Many studies on the effectiveness of isoflavones diet

against menopausal symptoms. In the current systematic review, it will be more focused on the effectiveness of soy isoflavones and red algae isoflavones facing menopause symptoms especially in the event of hot flushes

2 METHOD

Literature Search

This systematic review includes original journals discussing the effects of isoflavones on menopausal symptoms as outcomes in general but also in the measurements of hot flushes. Systematic literature searches are performed in major databases such as Proquest, Sciondirect and Scopus by entering isoflavones keywords, hot flushes, menopause. No other restrictions are used to maximize literature search. The list of literature references is done manually. The search results on the scopus database as many as 182 journals, ScienceDirect as many as 637 journals and Proquest 312 journals.

Criteria Inclusion

The criteria of inclusion of literature are random clinical trial (RCT) study on isoflavones effectiveness on hot flushes occurrence in postmenopausal women with years limit of 10 years (2007 - 2017). The research design of RCT must meet PICO criteria including the population used are menopausal women with both premenopausal, menopause transition, and post menopause with history of hot flushes > 4 times a day, intervention of isoflavones use as treatment can be extra pure soybean, combination and red clover. The comparison groups in the study consisted of at least two groups: the intervention group and the placebo group. The comparison groups in the study consist of two groups: the intervention group and the placebo group. All studies use English. Of the total journals of 1131 journals, there are 13 journals that match the criteria of inclusion of researchers and made material systematic review.

3 RESULTS

Literature Characteristic Systematic Review

From 13 journals, data collection is done in United States of America as much as 1 journal, Canada 1 journal, Korea 1 journal, Italy 3 journals, Brazil 2 journals, New Delhi 1 journal, Denmark 1 journal, Nepal 1, Austria 1 journal and Taiwan 1 journal. The

total sample in the literature was 1398 samples. A total of 3 journals involving Asian women, 9 journals involving western women (caucasian) and 1 journal involving multi-ethnic women are white spanish, white non spanish, Asian and African. All journals are journals with randomized control trial design designs with 8 journals using double blinded, 1 unblended journal, 1 journal of multicenter comparative study and 3 other journals not explaining in detail.

Isoflavones Intervention

From 10 journals, total of seven journals using pure soy extract with isoflavone dose of 70 mg (Fontvieille, Dionne and Riesco, 2017), 50,7 mg (Levis *et al.*, 2010), 90 mg (Carmignani *et al.*, 2010), , 60 mg (Franciscis *et al.*, 2017), 100 mg (Nahas *et al.*, 2007), 35 mg (Yang *et al.*, 2012), and 70 mg (Lee, Choue and Lim, 2017), and 80 mg (Ferrari, 2009). Two journals used combined soybean extract with isoflavone dose of 70.56 mg, and 80 mg (Davinelli *et al.*, 2017). One journal uses 30 mg of genestein (Evans *et al.*, 2011).

Two journals using red clover with isoflavones of 37.1 mg / d (Lambert *et al.*, 2017), 80 mg (Lipovac *et al.*, 2012), 60.8 mg mg One journal combination of 60.8 mg soy isoflavones and 19.2 mg red algae isoflavones (Mainini G, 2013). Characteristics of isoflavones dose can be seen in table 2.

Measuring Hot Flushes

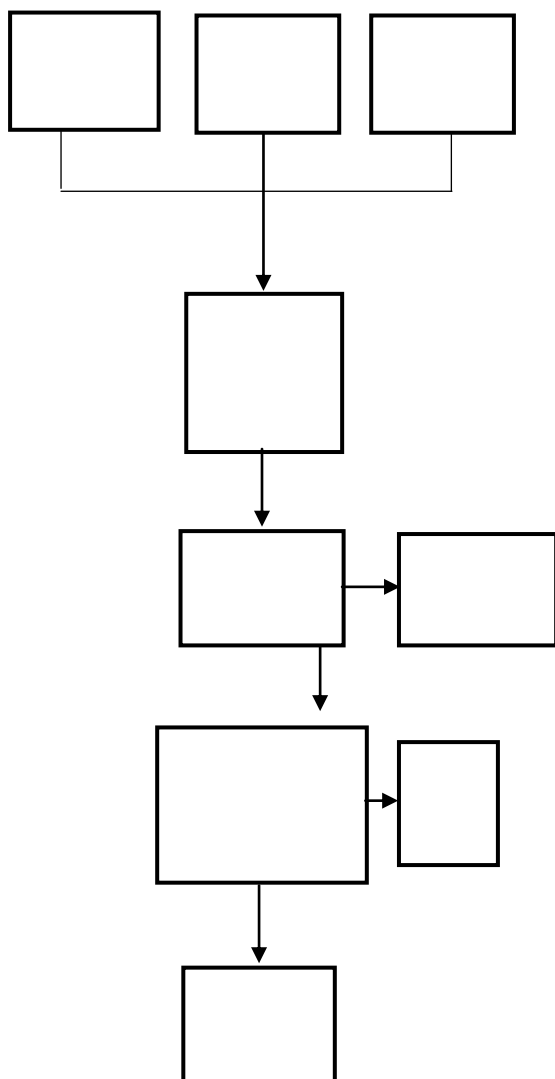
Measurement of hot flushes analysis in one journal using matlab software. As for other journals, hot flushes are always measured along with other components. Existing measuring instruments are usually a combination of menopausal symptoms. However, in each measurement there are several journals that include hot flushes diary to record hot flushes every day. Measurements used in the journal include Kupperman index used to assess vasomotor symptoms of menopausal women including hot flushes, Menopause Rating Scale (MRS) is used to evaluate the symptoms of menopause divided into 3 sub-somatic somatic (including hot flushes), psychological symptoms, and urogenital symptoms, Greene Climacteric Scale to measure psychological, vasomotoric, somatic, depression and anxiety on the subject, and Cooperman's index questionnaire

The influence of isoflavones on hot flushes

The results of the journal analysis revealed 9 out of 10 journals using extra pure soy intervention with isoflavones of 50.7 mg, 90 mg, 80 mg, 60 mg, and

100 mg, combined soybean intervention combined with isoflavones 70.56 mg, 60 mg, 80 mg the 30 mg genistein intervention showed a decrease in the incidence of hot flushes in postmenopausal women.

Figure 1. Process selection of Paper



From 2 journals, 1 journal with intervention of red algae isoflavones as much as 80 mg showed decreased incidence of hot flushes in menopausal women. While the combined intervention between soy isoflavones 60.8 mg and isoflavones 19.2 mg. The value of hot flushes decrease can be seen in table 1.

Table 1. The Value of Hot Flushes Decreased

Author	Decreased of Hot Flushes
Lee, H. et all. (2017) Extra soybean tablets	Positive Significant to intervention group 2.73±2.60
Fontvieile, A. (2017) Extra soybean tablets	Negative ρ=0.131
Franciscis, P. et all (2017) Extra soybean tablets	Positive Significant to ntervention group from 4.31 to 2.12
Davinelli, et all (2016) Fermentation of soybean	Positive ρ<0.001
Yang, T (2011) Extra soybean tablets	Negative ρ=0.506
Levis (2010) ekstra protein kedelai	Positive Significant to ntervention group 12.15±6.61
Carmignani (2010) Extra soybean tablets	Positive ρ=0.01
Evans (2010) Tablet genistein	Positive ρ=0.009
Ferrari (2009) Extra soybean tablets	Positive Significant to intervention group 41.2%
Nahas (2007) Extra soybean tablets	Positive ρ<0.001
Lambert, M. et all (2017) Extra red clover	Negative ρ=0.18
Lipovac (2012) Capsule of red clover	Positive ρ<0.0001
Mainini (2012) Suplement of red clover and soybean	Positive ρ<0.05

4 DISCUSSION

Isoflavones contained in soy extract and red clover extract (Lambert *et al.*, 2017). Research with intervention of extra isoflavones of pure soybean, genistein and combined soy isoflavones resulted in a significant reduction in the incidence of menopausal hot flushes. The structure of soybeans has an equation with 17 B-estradiol, the female main sex hormone (Thomas *et al.*, 2014)

Based on the analysis of 10 journals, extra isoflavones of soybeans are in the range of 30-100 mg. There is one journal using combined monoteraphy genistein, with the result that it decreases the incidence of hot flushes in the intervention group by 51% with p = 0.009 (Lambert *et al.*, 2017). There are 3 studies using the same extra soy as much as 200 mg but with different isoflavones ie 1 journal containing 50.7 mg and 2

journals containing 80 mg with different population numbers. The 12 week intervention in a sample of 60 Italian women resulted in a significant decrease in the incidence of hot flushes by 74.3%. The 24-week intervention in a sample of 248 multiethnic women resulted in a decrease in hot flushes with a standard deviation of 12.58 + 6.87. The 12 weeks intervention in a sample of 120 Italian women showed a decrease in hot flushes in the intervention group by 41.2%.

Based on the analysis of these results showed the limit of extra consumption of soybeans in its role reduce the incidence of hot flushes in menopausal women more than 70 mg / day. This is in line with the statement of the European Food Safety Authority (EFSA) which confirms that the consumption of at least 150 mg of extra soy isoflavones daily for 3 years can increase hormones in sensitive tissues such as in breast, endometrium and gland tyroid (Schmidt *et al.*, 2016).

In addition to being found in soybeans, isoflavones are also present in red clover. Soybean has 3 main structures of isoflavones in the form of glycoside ie genistin, daidzin and glycitin. While the main structure of red clover is 4 isoflavones including formononetin, biochanin A, daidzein and genistein. Both act as estrogenic in the female body (Jacobs *et al.*, 2009).

A study by Lambert *et al.* on the administration of extra red clover isoflavones combined with

probiotics showed no significant difference between the placebo group and the intervention with $p = 0.18$. This study uses extra red clover which is combined as much as 13.5 liters and consumed for 90 days with isoflavones content of 37.1 mg / d. This study describes hot flushes as primary outcomes and assessment of the respondent to the time of the sleep cycle.

The average characteristics of the study sample were women aged 40-60 years. A decrease in the incidence of hot flushes with intervention of more than 12 weeks gave more valid results compared to shorter duration (Schmidt *et al.*, 2016) Of the 13 journals, there are 4 journals with female populations focusing on women with post menopausal, 1 journal with pre menopausal population and other journals based on female age between 40-60 years unnoticed. Level of characteristic of menopause level can be seen in table 3 Characteristics of menopausal level of research sample. Women with pre menopause can cause a higher placebo response than women with post menopause (Liu and Eden, 2007).

The use of soy isoflavones and red algae to control the incidence of hot flushes in menopausal women requires an evaluation of the impact on women's health. The limitation of this systematic review is the difficulty of comparing results with diverse interventions, ranging from doses, compositions and measuring instruments

Table 2. The Dose of Isoflavones In the Study

Author	Intervention			Dose per day	Isoflavones per day	Decreased of hot flushes
	Isoflavones	Additives	Other intervention			
Lee, H. <i>et al.</i> (2017) Extra soybean tablets	35.28 mg	Lactose powder 15.6%, silica dioxide (0.5%) and magnesium stearate (0.5%)	-	2	70.56 mg	positive
Fontvieile, A. (2017) Extra soybean tablets	17.5 mg	-	Physic exercise	4	70 mg	negative
Franciscis, P. <i>et al.</i> (2017) Extra soybean tablets	60 mg	Lactobacillus 109 spores, 50 mg ekstra magnolia officanilus, 40 mg ekstrak vitex agnus castus, 35 mg vitamin D	-	1	60 mg	positive
Davinelli, <i>et al.</i> (2016) Fermentation of soybean	80 mg	25 mg resveratrol from vitis vinifera	-	1	80 mg	positive
Yang, (2011) Extra soybean tablets	17.5 mg	-	-	2	35 mg	negative
Levis (2010) ekstra protein kedelai	49,5+2.2 mg	-	-	1	51.7 mg	positive
Carmignani (2010) Extra soybean tablets	45 mg	-	-	2	90 mg	positive
Evans (2010) Tablet genistein	-	-	30 mg genistein	1	30 mg	positive
Ferrari (2009)	80 mg	-	-	1	80 mg	positive

Extra soybean tablets						
Nahas (2007) Extra soybean tablets	100 mg	-	-	2	100 mg	positive
Lambert, M. et all (2017) Extra red clover	37.1 mg/d	-	-	Not specific	Not specific	negative
Lipovac (2012) Capsule of red clover	80 mg	-	-	1	80 mg	positive
Mainini (2012) Suplement of red clover and soybean	60.8 mg	-	-		60.8 mg	positive

Table 3. Characteristic Level of Menopause Study Sampl

Author	Age of Study Sample	Menopause Level	Total Sample	Decreased of Hot Flushes
Lee, H. et all. (2017) Extra soybean tablets	45-60	Not Specific	84	Positive
Fontvielle, A. (2017) Extra soybean tablets	50 -70	Post Menopause	31	Negative
Franciscis, P. et all (2017) Extra soybean tablets	Not Specific	Post Menopause	180	Positive
Davinelli, et all (2016) Fermentation of soybean	50-55	Menopause	60	Positive
Yang, T (2011) Extra soybean tablets	Not Specific	Menopause	130	Negative
Levis (2010) ekstra protein kedelai	45-60	Peri Menopause	248	Positive
Carmignani (2010) Extra soybean tablets	40-60	Menopause	60	Positive
Evans (2010) Tablet genistein	45-65	Menopause	84	Positive
Ferrari (2009) Extra soybean tablets	40-65	Not Specific	120	Positive
Nahas (2007) Extra soybean tablets	Rate 55,1	Not Specific	80	Positive
Lambert, M. et all (2017) Extra red clover	40-65 Tahun	Peri Menopause	62	Negative
Lipovac (2012) Capsule of red clover	>40	Post Menopause	109	Positive
Mainini (2012) Suplement of red clover and soybean	Not Specific	Post Menopause	150	Positive

5 CONCLUSION

Systematic review of the effects of isoflavones on hot flushes occurrence in menopausal women provides a solution for further research. In a randomized control trial study, there will be 2 groups: the placebo group and the intervention group, to avoid a higher placebo response, it is necessary to have participant criteria, in a homogeneous level of menopause

Giving extra isoflavones to soybeans in either pure form or combination and red clover isoflavones positively impacted the decrease in the incidence of hot flushes in postmenopausal women but a similar study was required with larger numbers of samples and corresponding measuring instruments. Use of hot flushes as outcomes primary provides a more specific assessment of hot flushes variable.

The implication that can be taken is to know about alternative actions in reducing hot flushes. Nursing paradigm with 4 pillars of human in the sense of menopausal women, environment is defined as an environment that provides a choice of attitudes in menopausal women, health illness is defined as how the experience of menopausal women in the face of menopausal symptoms in the form of adaptive or maladaptive and nurse is defined as how the nurse see this phenomenon. Interventions given to women who are menopausal need to be informed to maintain reproductive health.

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