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Evaluation of the Potential Antidepressant Effects of Soybean Isoflavones

Mark Messina, PhD[*] and

Nutrition Matters, Inc. Pittsfield, MA, Tel: 413-464-0565

Carey Gleason, PhD

University of Wisconsin School of Medicine and Public Health, Tel: (608) 280-7000

Abstract

Objective—To determine whether isoflavones affect depressive symptoms in women.

Methods—Literature searches were conducted to identify clinical and epidemiologic studies that evaluated the impact of soy intake and isoflavone exposure on depressive symptoms. References from identified studies were also evaluated to identify eligible studies.

Results—Only limited epidemiologic research has evaluated the impact of soy or isoflavone intake on depression although several studies from China and Japan did find soy product intake was inversely related to risk of depression. However, often times, soy was evaluated only as a component of a summative dietary pattern (e.g., a “Japanese” or “Healthy” diet). Of the 20 intervention studies identified, roughly half found statistically significant reductions in depressive symptoms in response to isoflavones although several had design weakness. Of those studies reporting a lack of antidepressant effects of isoflavones, design limitations likely contributed to the lack of efficacy. In all but two trials, assessment of depression was, however, a secondary outcome. It is notable that both trials in which depression was a primary outcome found isoflavones significantly improved symptoms.

Conclusions—Although the data are inconsistent and limited, the clinical and epidemiologic evidence suggests that isoflavones may offer a safe, well-tolerated option for management of depression. Furthermore, the intervention doses used in the clinical studies fall well within the dietary range. The extant literature reveals key design features for future studies, which based upon the results of this review, are clearly warranted.

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Soybean isoflavones are purported to have a number of health benefits. Although still speculative, the conclusion of this review is that the epidemiologic and clinical evidence indicates improvements in mental health may be one of them.

Keywords

isoflavones; mental health; depression; soy; diet; clinical trials; epidemiology

[*]Corresponding author.

Conflicts: MM regularly consults for companies that manufacturer and/or sell soyfoods and/or isoflavone supplements

Introduction

Depression is a commonly occurring disorder associated with diminished quality of life and increased morbidity and mortality.[1,2] The World Health Organization (WHO) ranks depression as the fourth leading cause of disability worldwide and projects that by 2020, it will be the second leading cause.[3] Importantly, morbidity and mortality associated with chronic diseases such as coronary heart disease and cancer are more prevalent among individuals who are depressed.[4,5] Depression is an especially key concern for females; in fact, depression was recently cited as one of the 11 most important health issues facing peri- and postmenopausal women.[6] Younger people are also subject to depression; among US college students, 13.5% reported that depression adversely affected their academic performance.[7] Altogether, depression is a major health concern, affecting individuals across the lifespan. This point is certainly supported by the recent recommendation of the US Preventive Services Task Force to screen for depression among all adults.[8]

Epidemiologic studies indicate that many depressed individuals do not seek treatment for their condition,[9] and that fewer than half of those treated with pharmaco- and psychotherapies, achieve remission.[10] Adherence is low for a combination of reasons, including patient and provider factors, and medication side effects.[11] Thus, there is a need for identifying lifestyle approaches that can help to prevent the development of depression and reduce existing depressive symptoms.

There is emerging evidence that diet may be one such approach. Recently, a group of academics concluded that “diet is as important to psychiatry as it is to cardiology, endocrinology, and gastroenterology.”[12] A number of dietary patterns, foods and nutrients, and dietary constituents have been linked with mental health. One class of dietary constituents that has received attention in recent years for its possible antidepressant effects is isoflavones, compounds which are found primarily in soyfoods. The current paper reviews the impact of soy and isoflavone intake on depression, with an emphasis placed on the clinical research. Before reviewing this relationship, background information on diet and depression and isoflavones is provided.

Prevalence of depression

According to the WHO 350 million people suffer from depression[13] although rates of depression differ markedly among countries and regions of the world.[14] An analysis by Moussavi et al.[15] of the World Health Survey across 60 countries, found that the 12-month prevalence for ICD-10 (10th revision of the International Statistical Classification of Diseases and Related Health Problems) diagnosis of depressive episode averaged 3.2% in participants without comorbid physical disease and 9.3 to 23.0% in participants with chronic conditions. Ferrari et al.[14] reported that in 2010, depressive disorders were the second leading cause of years lived with disability (YLD); major depressive disorder (MDD) accounted for 8.2% (5.9-10.8%) of global YLDs and dysthymia for 1.4% (0.9-2.0%).

In the United States, the estimated prevalence of depression varies widely but appears to be increasing. For example, data on adults aged 18 years and older who participated in the 2006

Behavioral Risk Factor Surveillance System (BRFSS) (n=198,678) reveal a depression prevalence of 9.68% versus a prevalence of 6.13% among 4,800 individuals who participated in the 2005-2006 National Health and Nutrition Examination Survey (NHANES).[16] Although, both surveys used the 8-item Patient Health Questionnaire to detect depression, the studies differed in administration methods. The BRFSS used computer-assisted telephone interviewing whereas NHANES used computer-assisted personal interviewing. When medication usage is used as an indicator, the data suggest that prevalence of depression in the United States is rising; the rate of antidepressant treatment increased from 5.8% in 1996 to 10.1% in 2005 or from 13.3 to 27.0 million persons.[17]

Strikingly, there is an approximate two-fold female-male disparity in the prevalence of depression.[18] Beyond gender, a number of other sub-population groups have been identified as being at greater risk for depression. For example, the prevalence of depression is higher among US whites than blacks.[19] Also, individuals who are separated or divorced have significantly higher rates of major depression than the currently married.[20,21] Evidence indicates that younger people are affected by depression similar to adults. A nationally representative survey of 10,123 US adolescents aged 13 to 18 years found that lifetime and 12-month prevalence of MDD were 11.0% and 7.5%, respectively and corresponding rates of severe MDD were 3.0% and 2.3%, respectively.[22]

Finally, age also influences risk of having major depression as the prevalence generally goes down with age.[20,21] Aging does bring numerous risk factors for depression, including chronic medical illnesses, alterations in neurotransmitters resulting from neurological diseases like Parkinson's and Alzheimer's disease, and numerous psycho-social changes (e.g., caregiving, loss of support systems and role changes).[23] Nevertheless, in general happiness increases as we age; thus prevalence of depression declines.[21]

Diet and Depression

As noted at the onset, there is an increasing recognition of a link between diet and mental health. Fittingly, a set of dietary recommendations for the prevention of depression was recently issued by a group of Australian and European investigators.[24] These recommendations, however, do not seem to be specific to depression as they are similar to the general recommendations for a healthy diet. The recommendation to eat fruits and vegetables for the prevention of depression noted by Opie et al.[24] is supported by the results of a recent meta-analysis of observational studies involving over 200,000 individuals.[25] An earlier publication by Opie et al.[26] concluded that “effective dietary interventions were based on a single delivery mode, employed a dietitian and were less likely to recommend reducing red meat intake, select leaner meat products or follow a low-cholesterol diet.”[26]

Although Opie et al.[24] emphasized the importance of recognizing that antidepressant effects of diet are likely to come from the “cumulative and synergic effect of nutrients that comprise the whole-diet, rather than from the effects of individual nutrients or single foods,” the intake of a number of individual dietary constituents has been associated with depression. For example, an analysis of over 40,000 women participating in the Iowa Women's Health Study found that women who consumed <400 IU/day of vitamin D had significantly lower mental health-related quality of life compared to those who consumed ≥400 IU/day.[27] Also,

a 2015 systematic review and meta-analysis found that low serum folate and vitamin B12 levels are associated with depression in the aged although the association with the latter may only exist for women.[28]

A Japanese study which included 537 men and women aged 20-68 years found green tea and coffee consumption was inversely related to depressive symptoms, a benefit which could result from caffeine exposure.[29] Fish consumption may also be protective against depression according to the results of a meta-analysis of 26 epidemiologic studies.[30] The benefit of fish may be due to the greater intake of the long-chain omega-3 fatty acids since eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may exert anti-inflammatory effects[31] and some evidence indicates that inflammation is involved in the etiology of depression, although the exact role of and mechanisms associated with inflammation remain to be determined.[32-34] Interestingly, a recent Japanese cross-sectional study found that even among a population with higher blood levels of long-chain omega-3 fatty acids, serum levels of EPA and DHA were inversely associated with depressive symptoms in community dwellers.[35] In contrast, a recent Cochrane review found only a modest benefit of omega-3 fatty acid supplementation.[36]

The finding that fish intake is protective against depression and that low serum vitamin B12 levels increase risk is interesting in light of the findings by Beezhold et al.[37,38] that following a vegetarian diet is associated with healthy mood states given the lack of fish consumption by those adhering to this dietary pattern and that vegetarian vitamin B12 levels are lower than that of omnivores.[39] In one study by this group, the intake of both the omega-6 essential fatty acid linoleic acid and the omega-3 essential fatty acid alpha-linolenic acid was associated with better mood.[37] A pilot study by these authors reported that restriction of meat, fish, and poultry in omnivores improved some domains of short-term mood state.[40] However, a number of other studies report vegetarians are more likely to be depressed and have mental health issues although there appears to be little causal connection between vegetarian dietary pattern and depression.[41-46]

The type and amount of dietary carbohydrate may affect depression according to the results of the Women's Health Initiative Observational Study.[47] Among, approximately, 70,000 women participating in this study, a higher dietary glycemic index was associated with increasing odds of incident depression. Progressively higher consumption of dietary added sugars was also linked to increased risk whereas higher consumption of lactose, fiber, nonjuice fruit, and vegetables was significantly protective against depression. The connection between diet and depression may exist at least in part because of the effects of diet on the microbiome.[48] According to Dash et al.,[49] “there is compelling preclinical evidence that the gut microbiota can influence behaviors of relevance to anxiety, and that manipulation of the gut microbiota with specific probiotics or with antibiotics can influence depression-like behaviors.”

Finally, it is important to consider the possibility that reverse causality could underlie associations between diet and depression noted in epidemiologic studies.[50] That is, a change in dietary choices could be prompted by depressive symptoms. Diminished appetite is a symptom of major depression for many and there is also evidence that some people with

depression are more likely to consume high-fat and high-sugar foods[51] and fewer fruits and vegetables than their non-depressed counterparts.[52] However, an analysis of data from the Personality and Total Health (PATH) Through Life Study found that while current depression is associated with poorer dietary habits, a history of depression may prompt healthier dietary behaviors in the long term. Consequently, the authors of this analysis concluded that "clinicians should advocate dietary improvement for their patients with depression and should not be pessimistic about the likelihood of adherence to such recommendations."[50]

Hormones and Depression

The higher prevalence of depression among women compared to men suggests that reproductive hormones may be involved in the etiology of this disease. To this point, changes in estradiol and progesterone are thought to precipitate postpartum depression, which affects at least 10% of childbearing women.[53] Also, longitudinal studies suggest that menopause is a period of risk for new onset or recurrent depression for some women.[54-56] According to Freeman et al.,[57] both hot flashes and depressive symptoms occur early in the menopausal transition, although depressive symptoms are more likely to precede hot flashes, suggesting dissociation between climacteric symptoms and depression.

In support of a hormonal involvement in the development of depression is the conclusion of a meta-analysis of clinical studies that hormone therapy is effective in reducing depressed mood among peri- and postmenopausal women.[58] Although a subsequently published narrative review reached a similar conclusion,[59] and a recent large trial found a reduction in depressive symptoms in response to one form of hormone therapy,[60] the data are not consistent in this regard.[61]

The possible role of hormones in the etiology of depression and the efficacy of estrogen for the treatment of this disease, at least in peri- and postmenopausal women, provide grounds for speculating that soybean isoflavones may affect mental health overall and depression in particular

Isoflavones

Among commonly consumed foods, only the soybean contains physiologically relevant amounts isoflavones. This point is illustrated by the mean daily isoflavone intake of 30 to 50 mg among older individuals in Japan[62] whereas in the United States[63] and Europe,[64] per capita intake is less than 3 mg. Isoflavones have a similar chemical structure to estrogen, bind to estrogen receptors (ERs), and exert estrogen-like effects under certain experimental conditions. For these reasons, they are classified as phytoestrogens.[65] However, isoflavones are also classified as selective estrogen receptor modulators (SERMs).[66] SERMs, which include the breast cancer chemotherapies tamoxifen and raloxifene, are selective for tissue type; depending upon the tissue they can have estrogen agonistic effects, antagonistic effects, or no effects at all even in tissues affected by estrogen. Tissue selectivity is thought to be at least partly due to isoflavones' preferential binding to and activation of ERβ in comparison to ERα.[66]

These two ERs have different tissue distributions and often perform divergent and at times opposing functions in the body when activated. For example, in breast tissue, ERβ activation appears to inhibit the stimulatory and proliferative effects of ERα activation.[67] There are numerous clinical examples of isoflavones exerting estrogen-like effects in some tissues[68] but having no effect on other estrogen-sensitive endpoints,[69] although there is limited evidence demonstrating anti-estrogenic effects.[70-72] In addition to the classic estrogen receptors, isoflavones bind to and activate G protein-coupled estrogen receptor 1 (GPER), formerly referred to as G protein-coupled receptor 30 (GPR30).[73,74] The activation of GPER may be relevant in a discussion of depression because there is some evidence that the activation of this seven-transmembrane estrogen receptor plays a role in the antidepressant effects of estrogen.[75,76]

The isoflavones in soybeans and unfermented soyfoods are present primarily as glycosides; fermentation converts the glycosides to aglycones to varying degrees.[77] It is unclear whether isoflavone form impacts biological activity, but there is often confusion about the amount of biologically-active isoflavones in a food, since the sugar accounts for 40% of the weight of the glycoside. The recommended approach and the approach used in this article when referring to an amount of isoflavones is to refer to the aglycone equivalent weight.

When all forms of the individual isoflavones are considered, the three isoflavones (genistein, daidzein, and glycitein) account for approximately 50%, 40%, and 10%, respectively, of the total soybean isoflavone content.[77] Each of the three soybean isoflavones is a distinct chemical entity with different binding affinities for ERs; but for most endpoints genistein is considered to be the most potent isoflavone.[78] For example, Taku et al.[68] found that only soybean isoflavone supplements providing sufficient genistein alleviated menopause-related hot flashes.

Finally, traditional soyfoods contain approximately 3.5 mg of isoflavones per gram of protein;[62] highly processed soy can lose as much as 80% of its isoflavone content.[77] On average, traditional soyfoods contain 20–30 mg of isoflavones per serving (for example, 250 ml of soy milk made from whole soybeans or 100 g of tofu), and older-adult Japanese and Shanghai Chinese consume about 30–50 mg/d of isoflavones.[62]

Soy intake and depression: Epidemiologic studies

Several epidemiologic studies have investigated the relationship between soyfood intake and depression although many did so only as part of an overall dietary pattern. Importantly, with one exception, these studies involved populations of either Japanese or Chinese ethnicities. The only non-Asian exception is a US cross-sectional study which found no relation between total and individual urinary isoflavone excretion and depression among 193 postmenopausal women.[79] However, because of the extremely low isoflavone intake of Americans[63] this study provides little insight into the possible antidepressant effects of soyfoods or isoflavones.[80]

In contrast to this study, a multivariate analysis of data collected in a large cross-sectional study from China involving 11,473 men and women at least 35 years of age found that weekly consumption of beans or bean products was negatively associated with depressive

symptoms.[81] More specifically, the odds ratio (OR) plus 95% confidence intervals (CI) associated with rarely consuming legumes versus consuming legumes 2-3 times per week (reference) was 1.78 (1.49, 2.13, p<0.001). Risk of depression did not differ between high consumption of legumes (≥4 times per week) and moderate consumption (2-3 times per week). Although not specified in this paper, in Chinese population studies bean and bean products typically refer to soybean and soybean-derived products.

This point is illustrated by a cross-sectional study involving 1717 residents aged ≥65 years of age from rural Northeast China which found soy inversely related to risk of depression. Individuals consuming soybeans or soybean products ≥4 times/week were significantly less likely (3.6 vs. 12.5%, P<0.05) to have depressive symptoms than those rarely consuming soy products.[82] Multiple logistic regression analysis revealed that in comparison to those rarely consuming soy, the OR (95% CI) for depression for those consuming soybeans and soy products 2-3 times per week and ≥4 times/week were 0.36 (0.15, 0.87, p=0.23) and 0.50 (0.34, 0.74, p=0.001), respectively. It is unclear however to what extent confounding variables were controlled for in this analysis.

Two other studies were identified that examined diet and depression among ethnic Chinese, one from Hong Kong and one from Taiwan. Tsai et al.[83] found no relationship between legume intake (≥3×/week vs. <3×/week) and risk of depression after four years of follow up in a prospective study involving 1,609 older Taiwanese men and women. In contrast, a cross-sectional study from Hong Kong involving 3,999 older men and women found, using logistic regression analyses, that isoflavone intake was inversely related to Geriatric Depression Scale score.[84]

The remaining studies, all of which are from Japan, produced mixed results.[85-91] In a small cross-sectional study involving 89 peri- and postmenopausal women, Nagata et al.[91] found soy intake was significantly inversely correlated with the Center of Epidemiologic Studies of Depression (CES-D) scale (r=-0.22, P=0.04). Diet was assessed by a semiquantitative food frequency questionnaire that included nine food items for soy products (miso soup, tofu, deep-fried tofu, fried bean curd, dried bean curd, fermented soy beans, houba-miso, soymilk, and boiled soy beans).

This study by Nagata et al.[91] is notable because in the remaining Japanese studies soy intake was assessed only as part of an overall dietary pattern. For example, in a cross-sectional study by Sugawara et al.[88] involving 791 community-dwelling individuals, 71 of whom were classified as having depression using a self-report, symptom checklist (CES-D), no relationship was found between dietary pattern and risk of depression. Four dietary patterns were identified: “healthy”, “Western”, “bread and confectionery”, and “alcohol and accompanying” (various foods, including noodles and shellfish) dietary patterns. Among the foods included in the “healthy” dietary pattern were tofu and the fermented soybean product natto, whereas miso consumption was inversely related to the other three dietary patterns.

There was also no relationship between diet and depression in a prospective study examining postpartum depression among 865 women.[87] A total of 121 women were classified as having depression and the three dietary patterns identified. The “healthy”, “Western” and

"Japanese" dietary patterns were established on the basis of 33 predefined food groups. However, of the 33 food groups the only soy product listed was miso soup, which not surprisingly was most closely identified with the Japanese diet. Pulses were also listed but since they were much more closely identified with the "healthy" compared to the "Japanese" dietary pattern, it isn't clear that non-miso soyfoods were part of this group.

In contrast to the results of the above two Japanese studies that looked at dietary pattern, a serious of studies using prospective data collected from Japanese municipal employees found a link between diet and mood. Emphasizing the need to examine whole-diet patterns, rather than macronutrients, Nanri et al.[92] found that a "Health Japanese Dietary Pattern," which included tofu and natto, was associated with depressive symptoms. Specifically, individuals in the highest tertile of Healthy Japanese Dietary pattern demonstrated a lower risk for depression, characterized as a CES-D score equal to or greater than 16 (OR=0.39, 95% CI: 0.23, 0.67). Nanri et al.[85] later expanded the analysis to include 40,752 men and 48,285 women, modified dietary characterizations and used suicide as the endpoint. During the four year follow-up period 249 cases of death by suicide (171 men and 78 women) were reported. Among both men and women, a 'prudent' dietary pattern characterized by a high intake of vegetables, fruits, potatoes, soy products, mushrooms, seaweed and fish was associated with a decreased risk of suicide. In an analysis including both men and women, the multivariable-adjusted hazard ratio of suicide for the highest vs. the lowest quartiles of the dietary pattern score was 0.46 (95% CI: 0.28, 0.75) (P for trend, 0.005). The Western and traditional Japanese dietary patterns were unrelated to risk.

In this series of analyses, the dietary patterns were derived from principal component analysis of the consumption of 134 food and beverage items ascertained by a food frequency questionnaire. The Western dietary pattern was characterized by high intake of meat, processed meat, bread, dairy products, coffee, black tea, soft drink, dressing, sauce and mayonnaise. The Japanese dietary pattern was characterized by high intake of salmon, salty fish, oily fish, seafoods other than fish and pickles.[93]

In agreement with this prospective study by Nanri et al.,[85] are the results of a cross-sectional study of 2266 employees aged 21-65 years from all areas of Japan participating in the Japanese Study of Health, Occupation and Psychosocial factors related Equity (J-HOPE).[86] Habitual diet was assessed by a validated brief self-administered diet history questionnaire. Participants with high scores for the balanced Japanese dietary pattern were significantly less likely to show probable mood/anxiety disorders (Japanese version of the Kessler Psychological Distress Scale, ≥9) with multivariate adjustment including socioeconomic status and job stress factors (OR=0.66; 95% CI: 0.51, 0.86, p for trend, 0.002). Furthermore, a highly significant difference between the first and third tertiles of this dietary pattern was observed in participants with active strain (high demand and high control) with low worksite support (8.5 vs. 5.2, P=0.011). Tofu was most closely associated with the balanced dietary patterns; however, tofu was also associated, although to a lesser extent, with the "fish consumption" dietary pattern. Natto was most closely with this dietary pattern, which was unrelated to mood/anxiety disorders.

Finally, using the same J-HOPE data, Nari et al.[90] found that low protein consumption in Japanese men was associated with more depressive symptoms, but only when restricted to plant protein. Specifically, with men in the lowest quartile of plant protein consumption as the reference, men in the highest quartile demonstrated a reduced risk (OR, 0.67; 95% CI: 0.50, 0.89; p=0.015) for elevated CES-D scores. Although not discussed, soy protein is a major contributor to plant protein among native Japanese.[62]

In total, the epidemiological data support an inverse association between dietary intake of isoflavones and depression. Given the complexity of assessing dietary exposure to individual nutritional factors, it is not surprising that several studies examined isoflavone exposure as part of an overall dietary pattern. Only limited information about soy and mental health can be gleamed from studies in which soy was analyzed only as part of an overall dietary pattern. Consequently, it is notable that of the five Asian studies[81-84,91] that focused specifically on soy or isoflavones, four reported antidepressant effects.[81,82,84,91]

Isoflavones and depression: Clinical studies

Table 1 includes 20 clinical trials conducted in 14 different countries in which the effects of isoflavones on depression in women were evaluated. The dose of isoflavones ranged from 12.5[94] to 120 mg/d[95] and the duration from six weeks[96,97] to two years.[95,98] Sixteen trials[94-108] utilized a parallel design, three a cross-over design[109-111] and one was open label study.[112] Only one of the 20 trials involved clinically depressed patients.[102]

Two trials administered treatment for an extended period, two years. One of these examined depressive symptoms, and the second quality of life (QoL). Findings from these long-term studies diverged. In the trial studying mood effects, Italian women given 54 mg/d genistein showed a decline in depressive symptoms as measured with the Zung Self-rating Depression Scale. Specifically, the mean score (± SD) decreased from 41.00 ± 8.00 at baseline to 36.00 ± 6.00 at year two, compared to no change in placebo group (41.00 ± 7.00 at baseline to 43.00 ± 7.00 at year two).[98] The difference in final values between groups was significant ($p<0.01$). In contrast, in US women given either 80 or 120 mg total isoflavones, there were no differences between treatment and placebo groups in scores on the psychosocial domain of the Menopause-Specific Quality of Life questionnaire.[95] Given the different outcome measures, comparisons of these study findings may be problematic.

An important design difference between these two trials is the intervention dose. Because the investigators opted to use a soy germ-derived isoflavone supplement,[113] the 80 and 120 mg isoflavones provided approximately 10 and 15 mg genistein, much less than the 54 mg/d genistein used in the Italian study.[98] As noted previously, genistein is generally considered to be the most potent of the three isoflavones in soybeans. A much shorter-term trial by Jou et al.,[97] which also used a soy germ-derived supplement, found no decrease in depressive symptoms in response to 70 mg/d isoflavones but did in response to 35 mg/d. However, this study lacked a placebo and no information on the means by which depressive symptoms were assessed was provided.

The only other trial that administered isolated genistein also failed to find statistically significant differences between groups.[103] However, the 30 mg/d dose used in this trial is

little more than half the amount used in the Italian study.[98] Furthermore, although there were no statistically significant differences, the score for depression determined by the Green Climatic Scale decreased by 46% (4.60 ± 3.40 to 2.48 ± 2.06) in the genistein group but by only 21% (4.45 ± 3.48 to 3.35 ± 3.55) in the placebo group. Given the lower dose and that this trial was only 12 weeks in duration the nonsignificant results are still intriguing.

One trial found that in response to 100 mg/d isoflavones there were marked decreases in depressive symptoms as assessed by the Hamilton Rating Scale for Depression (HAM-D), a widely-validated measure of depressive mood symptoms.[104] Over a 90-day period, scores decreased from 16.3 ± 5.4 to 6.9 ± 5.2 ($p<0.05$) and the number of participants with HAM-D scores ≥8 decreased from 42 (93.3%) to 13 (28.9%) ($p<0.05$). However, this study lacked a placebo group. In response to 35 mg/d isoflavones, Albert et al.[112] also found a statistically significant decrease in depressive symptoms; however, this was an open label study that lacked a placebo group and very little information about the means by which depressive symptoms were assessed was provided. In contrast to these studies, a small Brazilian 4-month study failed to find that isoflavones (80 mg/d) alleviated depression although with respect to presentation of the data, only the relative changes vs. the baseline were provided.[99]

As noted previously three studies in Table 1 utilized a cross-over design;[109-111] two of the three demonstrated favorable effects on mood. One of these trials intervened with a soy germ-derived isoflavone supplement (114 mg/d) and failed to find effects on depressive symptoms in breast cancer patients over a three-month period.[111] Depression was assessed by means of 13 questions querying mood, social behavior, and opinion of the future. In contrast, a 90-d study by Lipovac et al.[109] found that scores for depression assessed using the Hospital Anxiety and Depression Scale (HADS) only decreased from 6.91 ± 4.02 to 5.23 ± 3.65 in the placebo group but decreased from 6.91 ± 4.02 to 1.50 ± 2.06 in the isoflavone (80 mg/d) group (between group difference, $p<0.001$).[109] Note that the isoflavones used in this study by Lipovac et al.[109] were derived from red clover. The predominate isoflavones in red clover, biochanin A and formononetin, are converted in vivo to genistein and daidzein, respectively.[114] In the other cross-over study, final scores for the Beck Depression Index were 9.7 ± 6.9 and 7.6 ± 5.2 in the placebo and isoflavone (60 mg/d) groups, respectively (between group difference, $p<0.01$) and final scores for depression-anxiety using the Profile of Mood States for these groups were 15.3 ± 8.0 and 10.2 ± 7.8, respectively (between group difference, $P<0.001$).[110]

In contrast to the study by Lipovac et al.,[109] cited above, which found red clover-derived isoflavones reduced depressive, no benefit of red clover-derived isoflavones was observed by Tice et al.[107] Both trials were of the same duration and used similar isoflavone doses although the instrument used to measure depression differed (HADS vs. Green Climactic Scale). Another trial that used red clover-derived isoflavones also failed to find benefits of the intervention although in this case the psychosocial domain of the Menopause-Specific Quality of Life questionnaire was used to represent depression.[115]

Two additional trials in Table 1 failed to find effects of isoflavones on depression. In one, women were given either a placebo or 120 mg/d isoflavones for 16 weeks.[105] Scores for

depressive symptoms, which were assessed using the CES-D, decreased significantly in women taking isoflavones (34%) and the placebo (28%) but the difference between groups was not statistically significant. In the other negative trial, depression was measured using the Geriatric Depression Scale, Questionnaire on Life Satisfaction Modules and the Short Form-36.[106] There was little change in any metric compared to baseline values and there were no differences between groups. This study differs from the other trials listed in table 1 in that the women were much older; the age range and mean age was 60 to 75 and 66, respectively.

One trial evaluated the effect of isoflavones in women who were engaged in a six-month exercise program.[108] Quality of life was estimated by the Short Form-36 (SF-36) and Perceived Stress Scale-10 (PSS-10) questionnaires, and menopausal symptoms by the Kupperman index. At study end the SF-36 Physical Component Summary and almost all the SF-36 subscales except for role-emotional and mental health increased only in the exercise group taking isoflavones.

Two trials, both of which reported anti-depressant effects of isoflavones differ from the previously discussed trials in important ways. The pilot trial by Estrella et al.[102] is the only one to involve clinically depressed patients and to include a positive control (selective serotonin update inhibitors). They found that over a three-month period 100 mg/d isoflavones reduced depressive symptoms to a similar extent as sertraline (50 mg/d) and fluoxetine (10 mg/d) using the Hamilton and Zung Depression Scale and the Zung Self-Rating Scale. In addition, the combination of sertraline and isoflavones resulted in a greater reduction in symptoms than the other three individual treatments. A limitation of this trial is the lack of a placebo group (the investigators appropriately avoided the use of a placebo for clinically depressed patients). However, a placebo effect could not account for the superior performance of the combination treatment versus the individual treatments.

The other trial found that among Japanese peri and postmenopausal women, a very moderate dose (25 mg/d) of isoflavones consumed in aglycone form reduced depressive symptoms assessed by the HADS and also reduced anxiety as assessed by the Athens Insomnia Scale.[94] In contrast to the benefit of this dose, this eight-week trial found that a very low dose of isoflavones (12.5 mg/d) lacked efficacy. It is noteworthy that isoflavone exposure occurred via treatment and as a result of a likely background dietary intake of about 40 mg/d.[62]

Two of the remaining three trials that are included in Table 1 found significant decreases in depressive symptoms but all three are limited in their ability to provide insight into the effects of isoflavones as a result of their particular experimental designs.[96,100,101] For example, Ishiwata et al.[100] found that in Japanese non-equol producers 30 mg/d (but not 10 mg/d) equol significantly decreased depressive symptoms. Equol is a bacterially-derived metabolite of the isoflavone daidzein that is synthesized by approximately 25% of non-Asians and 50% of Asians; the difference resulting from cultural variations in intestinal bacteria.[116] The relevance of this finding to isoflavones is unclear.

Mucci et al.[101] found that a preparation containing 60 mg isoflavones significantly reduced depressive symptoms in postmenopausal women; however, also included in the preparation was *Lactobacillus sporogenes* (added to improve isoflavone absorption) and Magnolia extract. The active ingredients of Magnolia extract, magnolol and honokiol, interact with γ-aminobutyric acid system and exhibit a sedative central action useful for restoring the sleep balance.[117] Because isoflavones were not administered in isolation, it is not possible to know to what extent isoflavones contributed to the reduction in symptoms. In the third study, Wahner-Roedler et al.,[96] found that 20 g/d soy protein containing 160 mg isoflavones (100 mg aglycone) significantly decreased depressive symptoms in fibromyalgia patients but this effect did not differ from the response in patients consuming milk protein. How depression in patients with fibromyalgia relates to depression in healthy postmenopausal women is unclear.

Finally, two case reports provide support for a beneficial effect of isoflavones in management of psychiatric illnesses. In one, in response to the administration of soy isoflavones, a 48-year-old woman with a diagnosis of schizoaffective disorder experienced a dramatic improvement in her symptoms of persecutory ideas and depression (sadness of mood) over a period of one week that was sustained over the course of one year.[118] Furthermore, psychotic symptoms (in the absence of postmenopausal symptoms such as hot flashes) recurred on discontinuation but were again ameliorated on re-initiation of isoflavones. The second report also involves a women with diagnosis of schizoaffective disorder that included marked depressive symptoms which were unsuccessfully treated with paliperidone and escitalopram.[118] Because the depressive symptoms had worsened following hysterectomy, isoflavone supplementation was started on cessation of escitalopram. Symptoms improved during eight weeks of treatment. The patient was continued on the combination of paliperidone and isoflavones and improvement was maintained during the last follow-up at the end of six months. In addition to the usual design limitations associated with case-reports, the two discussed here lacked detailed information on the specific type and amount of isoflavone supplements used.

Altogether, more than half of the studies administering isoflavones found some degree of beneficial effects on mood. However, for reasons described below, the findings can only be described as intriguing and suggestive.

Discussion

Summarizing human studies assessing the mood-altering effects of isoflavones is complicated by a variety of factors, including differences in outcome assessment measures, enrollment of demographically and clinically diverse populations, variations in form and dose of isoflavone interventions, and important differences in study design, such as length of exposure and use of a control group.

Of the 20 trials in Table 1 that evaluated the mood and anti-depressant effects of isoflavones (or an isoflavone metabolite), nine found evidence of efficacy,[94,98,100-102,104,109,110,112] and a tenth found benefit at one dose but not another.[97] In addition to these ten trials the findings from one other trial are suggestive of benefit when considering the relatively low

intervention dose and short study duration.[103] The remaining nine studies showed no evidence of an effect of isoflavones on depression.[95,96,99,105-108,111,115]

In some instances, study design factors may account for the divergent findings. Two studies demonstrating no effect intervened with soy germ-derived isoflavones so exposure to genistein, the soybean isoflavone considered to be most potent, was minimal.[95,111] However, the open label trial by Albert et al.[112] and the unblinded trial by Jou et al.[97] also intervened with a soy germ-derived supplement and used relatively low doses, which suggests the improvement in the participants in these latter two studies was likely a placebo effect. In another trial,[108] all women engaged in an exercise program which could have masked an effect of isoflavones, since exercise exerts antidepressant effects.[119] Although the trial by Mucci et al.[101] showed an isoflavone-containing preparation was beneficial, the specific contribution of isoflavones cannot be determined because the intervention included a Magnolia extract.

Comparisons are further complicated between cross-over[109-111] and parallel-design studies,[94-108,112,115] and in some cases the absence of a placebo control group.[97,102,104,112] Perhaps related to study design, two studies experienced hjgh rates of dropout.[96,106] In four other trials, there is no obvious explanation for the lack of benefits.[99,105,107,115]

Another factor potentially influencing findings was the choice of outcome measure. In some instances mood was assessed in relation to menopause QoL[95,115] and climacteric symptoms.[103,107] While there is some overlap, measuring QoL in relation to menopausal symptoms is not equivalent to measuring general depressive symptoms. Another major limitation of the existing data is that in all but two trials depressive symptoms were secondary endpoints,[94,102] In some cases, studies may have been under-powered to address secondary aims. On the contrary, it is notable that both of the trials in which depression was the primary health outcome found isoflavones were efficacious: one involved depressed patients[102] and the other healthy menopausal women.[94]

The above distinction highlights how key dissimilarities in the study population may influence the efficacy of isoflavones on mood, including variations in age, menopausal status, and clinical diagnoses. The failure of Kok et al.[106] to find benefits could have been due to the older age of the study participants.[120,121] One trial failing to find a benefit of isoflavones involved fibromyalgia patients[96] and another enrolled breast cancer patients.[111] It is unclear whether depressive symptoms in fibromyalgia or breast cancer patients correspond to depressive symptoms in non-clinical populations. Some of the more interesting findings involved participants with psychiatric conditions (e.g., two case-reports of response in patients with schizoaffective disorders).

The findings by Estrella et al.[102] suggest that isoflavones augment the benefits SSRIs in depressed patients. Specifically, the combination of sertraline and isoflavones demonstrated greater improvements in mood compared to treatment with sertraline, fluoxetine or soy isoflavones alone. And, as already noted, a “placebo effect” could not explain why the combination of sertraline and isoflavones was more efficacious than the three individual treatments in this study. The combination effect is intriguing in light of research showing

estrogen therapy enhanced the efficacy of sertraline in older depressed women.[122] However, these effects may only be detected in a clinical population.

Several of the studies included in Table 1 enrolled women in the menopausal transition. Since isoflavones have been shown to alleviate menopausal-related hot flashes,[68] it is important to consider that through an effect on climacteric symptoms, depressive symptoms are reduced. Hot flashes and night sweats, especially the latter as a result of sleep disturbances, may adversely affect mood.[123] (A recently published Japanese cross-sectional study by Cui et al.[124] found a very pronounced positive relationship between isoflavone intake and sleep duration and sleep quality sleep[125]). The differing results by Tice et al.[107] and Lipovac et al.,[109] may provide some insight into this question as the former found no effect on hot flashes or depression whereas the latter found both symptoms were reduced.

However, a preliminary study found dissociation between mood and climacteric symptoms, such that estrogen therapies effectively treated perimenopausal depression independent of their beneficial effects on vasomotor symptoms.[126] In support of this finding are the results of the aforementioned Kronos Early Estrogen Prevention Study-Cognitive and Affective Study.[60] Although both oral and transdermal estrogen reduced hot flashes in postmenopausal women, only the former improved mood. Furthermore, there was no indication that in the study by Estrella et al.[102] the presence of hot flashes was involved in the etiology of clinical depression in study participants. In addition, in the study by Hirose et al.[94] the alleviation of hot flashes could not have contributed to the antidepressant effects of isoflavones since there was no difference in hot flashes between the low and high-dose isoflavone groups even though depression was reduced only in the latter.

Finally, as noted previously, the possible role of reproductive hormones in the etiology of depression and the efficacy of estrogen for the treatment of this condition provide grounds for speculating that soybean isoflavones may alleviate depression and/or prevent its onset. It follows therefore that perhaps isoflavones may be efficacious in peri- and postmenopausal women but not premenopausal women. The many studies discussed in this review that specified an age range that likely included some premenopausal women did not sub-analyze the data according to menopausal status.

Conclusions

While sparse and preliminary, data from human studies examining the potential mood effects of isoflavones are intriguing. More research is needed and warranted. As discussed above, the extant literature reveals key design features for future studies. It is recommended that trials should be at least 3 months in duration, have an appropriate control/placebo group, provide between 50 and 100 mg/d isoflavones (expressed in aglycone equivalents) and use an assessment instrument that is specifically designed to measure depression, as opposed to mood symptoms associated with menopause, or QoL measures.

Importantly, isoflavones at the doses used in the clinical trials in Table 1 have an impressive safety profile, especially compared to standardly prescribed therapies. In fact, after an extensive review of the scientific literature, the European Food Safety Authority recently

concluded that in peri- and postmenopausal women, isoflavones do not adversely affect the mammary gland, uterus, and thyroid gland, the three organs that were considered by the panel of experts and the organs that have been the subject of most controversy.[127]

In all of the trials in Table 1 isoflavones were provided in tablet form. However, the amount of isoflavones showing efficacy for reducing depressive symptoms can be ingested through the consumption of approximately two to four servings per day of traditional soyfoods. Therefore, both isoflavone supplements and soyfoods and a combination of both, exist as potential means of preventing and treating depression. Although the protein in soybeans can cause allergic reactions, allergy to soy protein is relatively rare among adults.[128] Isoflavones in tablet form would not be a concern in this regard. Altogether, there is intriguing preliminary data indicating that soy isoflavones could offer a safe, well-tolerated option for management of depression symptoms.

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References

1. Spijker J, Graaf R, Bijl RV, Beekman AT, Ormel J, Nolen WA. Functional disability and depression in the general population. Results from the Netherlands Mental Health Survey and Incidence Study (NEMESIS). Acta Psychiatr Scand. 2004; 110(3):208–14. [PubMed: 15283741]
2. Ustun TB, Ayuso-Mateos JL, Chatterji S, Mathers C, Murray CJ. Global burden of depressive disorders in the year 2000. Br J Psychiatry. 2004; 184:386–92. [PubMed: 15123501]
3. Murray, CJL.; Lopez, AD. The Global Burden of Disease: A Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Cambridge, MA: Harvard University Press; 1996.
4. Bush DE, Ziegelstein RC, Tayback M, et al. Even minimal symptoms of depression increase mortality risk after acute myocardial infarction. Am J Cardiol. 2001; 88(4):337–41. [PubMed: 11545750]
5. Pinquart M, Duberstein PR. Depression and cancer mortality: a meta-analysis. Psychol Med. 2010; 40(11):1797–810. [PubMed: 20085667]
6. van Dijk GM, Kavousi M, Troup J, Franco OH. Health issues for menopausal women: the top 11 conditions have common solutions. Maturitas. 2015; 80(1):24–30. [PubMed: 25449663]
7. Ross RW, Oh WK, Xie W, et al. Inherited variation in the androgen pathway is associated with the efficacy of androgen-deprivation therapy in men with prostate cancer. J Clin Oncol. 2008; 26(6): 842–7. [PubMed: 18281655]
8. Sui AL. Screening for depression in adults. US Preventive Services Task Force recommendation statement. JAMA internal medicine. 2016; 315(4):380–87.
9. Druss BG, Hoff RA, Rosenheck RA. Underuse of antidepressants in major depression: prevalence and correlates in a national sample of young adults. J Clin Psychiatry. 2000; 61(3):234–7. [PubMed: 10817113]
10. Casacalenda N, Perry JC, Looper K. Remission in major depressive disorder: a comparison of pharmacotherapy, psychotherapy, and control conditions. Am J Psychiatry. 2002; 159(8):1354–60. [PubMed: 12153828]
11. Masand PS. Tolerability and adherence issues in antidepressant therapy. Clin Ther. 2003; 25(8): 2289–304. [PubMed: 14512135]
12. Sarris J, Logan AC, Akbaraly TN, et al. Nutritional medicine as mainstream in psychiatry. The lancet Psychiatry. 2015; 2(3):271–4. [PubMed: 26359904]

13. World Health Organization. [Accessed April 10, 2016] Depression Fact Sheet. Revised April 2016. http://www.who.int/mediacentre/factsheets/fs369/en/
14. Ferrari AJ, Charlson FJ, Norman RE, et al. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 2013; 10(11):e1001547. [PubMed: 24223526]
15. Moussavi S, Chatterji S, Verdes E, Tandon A, Patel V, Ustun B. Depression, chronic diseases, and decrements in health: results from the World Health Surveys. Lancet. 2007; 370(9590):851–8. [PubMed: 17826170]
16. Li C, Ford ES, Zhao G, Tsai J, Balluz LS. A comparison of depression prevalence estimates measured by the Patient Health Questionnaire with two administration modes: computer-assisted telephone interviewing versus computer-assisted personal interviewing. International journal of public health. 2012; 57(1):225–33. [PubMed: 21523617]
17. Olfson M, Marcus SC. National patterns in antidepressant medication treatment. Arch Gen Psychiatry. 2009; 66(8):848–56. [PubMed: 19652124]
18. Van de Velde S, Bracke P, Levecque K. Gender differences in depression in 23 European countries. Cross-national variation in the gender gap in depression. Soc Sci Med. 2010; 71(2):305–13. [PubMed: 20483518]
19. Riolo SA, Nguyen TA, Greden JF, King CA. Prevalence of depression by race/ethnicity: findings from the National Health and Nutrition Examination Survey III. Am J Public Health. 2005; 95(6): 998–1000. [PubMed: 15914823]
20. Weissman MM, Bland RC, Canino GJ, et al. Cross-national epidemiology of major depression and bipolar disorder. JAMA. 1996; 276(4):293–9. [PubMed: 8656541]
21. Andrade L, Caraveo-Anduaga JJ, Berglund P, et al. The epidemiology of major depressive episodes: results from the International Consortium of Psychiatric Epidemiology (ICPE) Surveys. International journal of methods in psychiatric research. 2003; 12(1):3–21. [PubMed: 12830306]
22. Avenevoli S, Swendsen J, He JP, Burstein M, Merikangas KR. Major depression in the national comorbidity survey-adolescent supplement: prevalence, correlates, and treatment. J Am Acad Child Adolesc Psychiatry. 2015; 54(1):37–44 e2. [PubMed: 25524788]
23. Blazer DG 2nd, Hybels CF. Origins of depression in later life. Psychol Med. 2005; 35(9):1241–52. [PubMed: 16168147]
24. Opie RS, Itsiopoulos C, Parletta N, et al. Dietary recommendations for the prevention of depression. Nutr Neurosci. 2015
25. Liu X, Yan Y, Li F, Zhang D. Fruit and vegetable consumption and risk of depression: A meta-analysis. Nutr. 2015
26. Opie RS, O'Neil A, Itsiopoulos C, Jacka FN. The impact of whole-of-diet interventions on depression and anxiety: a systematic review of randomised controlled trials. Public Health Nutr. 2014:1–20. [PubMed: 24650538]
27. Motsinger S, Lazovich D, MacLehose RF, Torkelson CJ, Robien K. Vitamin D intake and mental health-related quality of life in older women: the Iowa Women's Health Study. Maturitas. 2012; 71(3):267–73. [PubMed: 22209201]
28. Petridou ET, Kousoulis AA, Michelakos T, et al. Folate and B12 serum levels in association with depression in the aged: a systematic review and meta-analysis. Aging & mental health. 2015:1–9.
29. Pham NM, Nanri A, Kurotani K, et al. Green tea and coffee consumption is inversely associated with depressive symptoms in a Japanese working population. Public Health Nutr. 2014; 17(3): 625–33. [PubMed: 23453038]
30. Li F, Liu X, Zhang D. Fish consumption and risk of depression: a meta-analysis. J Epidemiol Community Health. 2015
31. Kiecolt-Glaser JK, Belury MA, Andridge R, Malarkey WB, Hwang BS, Glaser R. Omega-3 supplementation lowers inflammation in healthy middle-aged and older adults: a randomized controlled trial. Brain Behav Immun. 2012; 26(6):988–95. [PubMed: 22640930]
32. Raison CL, Miller AH. Is depression an inflammatory disorder? Current psychiatry reports. 2011; 13(6):467–75. [PubMed: 21927805]
33. Berk M, Williams LJ, Jacka FN, et al. So depression is an inflammatory disease, but where does the inflammation come from? BMC Med. 2013; 11:200. [PubMed: 24228900]

34. Maes M, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro) inflammatory and oxidative & nitrosative stress pathways. Neuro endocrinology letters. 2011; 32(1):7–24. [PubMed: 21407167]
35. Horikawa C, Otsuka R, Kato Y, et al. Cross-sectional association between serum concentrations of n-3 long-chain PUFA and depressive symptoms: results in Japanese community dwellers. Br J Nutr. 2016; 115(4):672–80. [PubMed: 26689657]
36. Appleton KM, Sallis HM, Perry R, Ness AR, Churchill R. Omega-3 fatty acids for depression in adults. Cochrane Database Syst Rev. 2015; 11:CD004692.
37. Beezhold BL, Johnston CS, Daigle DR. Vegetarian diets are associated with healthy mood states: a cross-sectional study in Seventh day Adventist adults. Nutr J. 2010; 9:26. [PubMed: 20515497]
38. Beezhold B, Radnitz C, Rinne A, DiMatteo J. Vegans report less stress and anxiety than omnivores. Nutr Neurosci. 2015; 18(7):289–96. [PubMed: 25415255]
39. Pawlak R. Is vitamin B12 deficiency a risk factor for cardiovascular disease in vegetarians? Am J Prev Med. 2015; 48(6):e11–26. [PubMed: 25998928]
40. Beezhold BL, Johnston CS. Restriction of meat, fish, and poultry in omnivores improves mood: a pilot randomized controlled trial. Nutr J. 2012; 11(1):9. [PubMed: 22333737]
41. Michalak J, Zhang XC, Jacobi F. Vegetarian diet and mental disorders: results from a representative community survey. The international journal of behavioral nutrition and physical activity. 2012; 9:67. [PubMed: 22676203]
42. Larsson CL, Klock KS, Nordrehaug Astrom A, Haugejorden O, Johansson G. Lifestyle-related characteristics of young low-meat consumers and omnivores in Sweden and Norway. J Adolesc Health. 2002; 31(2):190–8. [PubMed: 12127390]
43. Baines S, Powers J, Brown WJ. How does the health and well-being of young Australian vegetarian and semi-vegetarian women compare with non-vegetarians? Public Health Nutr. 2007; 10(5):436–42. [PubMed: 17411462]
44. Perry CL, McGuire MT, Neumark-Sztainer D, Story M. Characteristics of vegetarian adolescents in a multiethnic urban population. J Adolesc Health. 2001; 29(6):406–16. [PubMed: 11728890]
45. Bas M, Karabudak E, Kiziltan G. Vegetarianism and eating disorders: association between eating attitudes and other psychological factors among Turkish adolescents. Appetite. 2005; 44(3):309–15. [PubMed: 15927731]
46. Burkert NT, Muckenhuber J, Grossschadl F, Rasky E, Freidl W. Nutrition and health - the association between eating behavior and various health parameters: a matched sample study. PLoS One. 2014; 9(2):e88278. [PubMed: 24516625]
47. Gangwisch JE, Hale L, Garcia L, et al. High glycemic index diet as a risk factor for depression: analyses from the Women's Health Initiative. Am J Clin Nutr. 2015; 102(2):454–63. [PubMed: 26109579]
48. Jiang H, Ling Z, Zhang Y, et al. Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun. 2015; 48:186–94. [PubMed: 25882912]
49. Dash S, Clarke G, Berk M, Jacka FN. The gut microbiome and diet in psychiatry: focus on depression. Current opinion in psychiatry. 2015; 28(1):1–6. [PubMed: 25415497]
50. Jacka FN, Cherbuin N, Anstey KJ, Butterworth P. Does reverse causality explain the relationship between diet and depression? J Affect Disord. 2015; 175:248–50. [PubMed: 25658499]
51. Whitaker KM, Sharpe PA, Wilcox S, Hutto BE. Depressive symptoms are associated with dietary intake but not physical activity among overweight and obese women from disadvantaged neighborhoods. Nutr Res. 2014; 34(4):294–301. [PubMed: 24774065]
52. Payne ME, Steck SE, George RR, Steffens DC. Fruit, vegetable, and antioxidant intakes are lower in older adults with depression. J Acad Nutr Diet. 2012; 112(12):2022–7. [PubMed: 23174689]
53. Bloch M, Daly RC, Rubinow DR. Endocrine factors in the etiology of postpartum depression. Compr Psychiatry. 2003; 44(3):234–46. [PubMed: 12764712]
54. Bromberger JT, Kravitz HM, Chang YF, Cyranowski JM, Brown C, Matthews KA. Major depression during and after the menopausal transition: Study of Women's Health Across the Nation (SWAN). Psychol Med. 2011; 41(9):1879–88. [PubMed: 21306662]

55. Freeman EW, Sammel MD, Lin H, Nelson DB. Associations of hormones and menopausal status with depressed mood in women with no history of depression. Arch Gen Psychiatry. 2006; 63(4): 375–82. [PubMed: 16585466]
56. Cohen LS, Soares CN, Vitonis AF, Otto MW, Harlow BL. Risk for new onset of depression during the menopausal transition: the Harvard study of moods and cycles. Arch Gen Psychiatry. 2006; 63(4):385–90. [PubMed: 16585467]
57. Freeman EW, Sammel MD, Lin H. Temporal associations of hot flashes and depression in the transition to menopause. Menopause. 2009; 16(4):728–34. [PubMed: 19188849]
58. Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. Psychoneuroendocrinology. 1997; 22(3):189–212. [PubMed: 9203229]
59. Grigoriadis S, Kennedy SH. Role of estrogen in the treatment of depression. Am J Ther. 2002; 9(6):503–9. [PubMed: 12424508]
60. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: Findings from the randomized, controlled KEEPS-Cognitive and Affective Study. PLoS Med. 2015; 12(6):e1001833. [PubMed: 26035291]
61. Yalamanchili V, Gallagher JC. Treatment with hormone therapy and calcitriol did not affect depression in older postmenopausal women: no interaction with estrogen and vitamin D receptor genotype polymorphisms. Menopause. 2012; 19(6):697–703. [PubMed: 22205149]
62. Messina M, Nagata C, Wu AH. Estimated Asian adult soy protein and isoflavone intakes. Nutr Cancer. 2006; 55(1):1–12. [PubMed: 16965235]
63. Bai W, Wang C, Ren C. Intakes of total and individual flavonoids by US adults. Int J Food Sci Nutr. 2014; 65(1):9–20. [PubMed: 24020353]
64. Zamora-Ros R, Knaze V, Lujan-Barroso L, et al. Dietary intakes and food sources of phytoestrogens in the European Prospective Investigation into Cancer and Nutrition (EPIC) 24-hour dietary recall cohort. Eur J Clin Nutr. 2012; 66(8):932–41. [PubMed: 22510793]
65. Sarkar FH, Li Y. Soy isoflavones and cancer prevention. Cancer Invest. 2003; 21(5):744–57. [PubMed: 14628433]
66. Oseni T, Patel R, Pyle J, Jordan VC. Selective estrogen receptor modulators and phytoestrogens. Planta Med. 2008; 74(13):1656–65. [PubMed: 18843590]
67. Speirs V, Carder PJ, Lane S, Dodwell D, Lansdown MR, Hanby AM. Oestrogen receptor beta: what it means for patients with breast cancer. Lancet Oncol. 2004; 5(3):174–81. [PubMed: 15003201]
68. Taku K, Melby MK, Kronenberg F, Kurzer MS, Messina M. Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. Menopause. 2012; 19(7):776–90. [PubMed: 22433977]
69. Alekel DL, Van Loan MD, Koehler KJ, et al. The soy isoflavones for reducing bone loss (SIRBL) study: a 3-y randomized controlled trial in postmenopausal women. Am J Clin Nutr. 2010; 91(1): 218–30. [PubMed: 19906801]
70. Sampey BP, Lewis TD, Barbier CS, Makowski L, Kaufman DG. Genistein effects on stromal cells determines epithelial proliferation in endometrial co-cultures. Exp Mol Pathol. 2011; 90(3):257–63. [PubMed: 21281625]
71. Murray MJ, Meyer WR, Lessey BA, Oi RH, DeWire RE, Fritz MA. Soy protein isolate with isoflavones does not prevent estradiol-induced endometrial hyperplasia in postmenopausal women: a pilot trial. Menopause. 2003; 10(5):456–64. [PubMed: 14501608]
72. Kayisli UA, Aksu CA, Berkkanoglu M, Arici A. Estrogenicity of isoflavones on human endometrial stromal and glandular cells. J Clin Endocrinol Metab. 2002; 87(12):5539–44. [PubMed: 12466350]
73. Thomas P, Dong J. Binding and activation of the seven-transmembrane estrogen receptor GPR30 by environmental estrogens: a potential novel mechanism of endocrine disruption. J Steroid Biochem Mol Biol. 2006; 102(1-5):175–9. [PubMed: 17088055]
74. Maggiolini M, Vivacqua A, Fasanella G, et al. The G protein-coupled receptor GPR30 mediates c-fos up-regulation by 17beta-estradiol and phytoestrogens in breast cancer cells. J Biol Chem. 2004; 279(26):27008–16. [PubMed: 15090535]

75. Estrada-Camarena E, Lopez-Rubalcava C, Vega-Rivera N, Recamier-Carballo S, Fernandez-Guasti A. Antidepressant effects of estrogens: a basic approximation. Behav Pharmacol. 2010; 21(5-6): 451–64. [PubMed: 20700047]
76. Xu H, Qin S, Carrasco GA, et al. Extra-nuclear estrogen receptor GPR30 regulates serotonin function in rat hypothalamus. Neuroscience. 2009; 158(4):1599–607. [PubMed: 19095043]
77. Murphy PA, Barua K, Hauck CC. Solvent extraction selection in the determination of isoflavones in soy foods. J Chromatogr B Analyt Technol Biomed Life Sci. 2002; 777(1-2):129–38.
78. Song TT, Hendrich S, Murphy PA. Estrogenic activity of glycitein, a soy isoflavone. J Agric Food Chem. 1999; 47(4):1607–10. [PubMed: 10564025]
79. Richard A, Rohrmann S, Mohler-Kuo M, et al. Urinary phytoestrogens and depression in perimenopausal US women: NHANES 2005-2008. J Affect Disord. 2014; 156:200–5. [PubMed: 24434020]
80. Messina M. Western soy intake is too low to produce health effects. Am J Clin Nutr. 2004; 80(2): 528–9. [PubMed: 15277184]
81. Zhou X, Bi B, Zheng L, et al. The prevalence and risk factors for depression symptoms in a rural Chinese sample population. PLoS One. 2014; 9(6):e99692. [PubMed: 24919087]
82. Yu S, Guo X, Yang H, Zheng L, Sun Y. Soybeans or soybean products consumption and depressive symptoms in older residents in rural Northeast China: A cross-sectional study. J Nutr Health Aging. 2015; 19(9):884–93. [PubMed: 26482689]
83. Tsai AC, Chang TL, Chi SH. Frequent consumption of vegetables predicts lower risk of depression in older Taiwanese - results of a prospective population-based study. Public Health Nutr. 2012; 15(6):1087–92. [PubMed: 22176686]
84. Woo J, Lynn H, Lau WY, et al. Nutrient intake and psychological health in an elderly Chinese population. Int J Geriatr Psychiatry. 2006; 21(11):1036–43. [PubMed: 16955432]
85. Nanri A, Mizoue T, Poudel-Tandukar K, et al. Dietary patterns and suicide in Japanese adults: the Japan Public Health Center-based Prospective Study. Br J Psychiatry. 2013; 203(6):422–7. [PubMed: 24115342]
86. Suzuki T, Miyaki K, Tsutsumi A, et al. Japanese dietary pattern consistently relates to low depressive symptoms and it is modified by job strain and worksite supports. J Affect Disord. 2013; 150(2):490–8. [PubMed: 23759276]
87. Okubo H, Miyake Y, Sasaki S, Tanaka K, Murakami K, Hirota Y. Dietary patterns during pregnancy and the risk of postpartum depression in Japan: the Osaka Maternal and Child Health Study. Br J Nutr. 2011; 105(8):1251–7. [PubMed: 21144112]
88. Sugawara N, Yasui-Furukori N, Tsuchimine S, et al. No association between dietary patterns and depressive symptoms among a community-dwelling population in Japan. Annals of general psychiatry. 2012; 11(1):24. [PubMed: 23006931]
89. Nanri A. Nutritional epidemiology of type 2 diabetes and depressive symptoms. J Epidemiol. 2013; 23(4):243–50. [PubMed: 23748249]
90. Nanri A, Eguchi M, Kuwahara K, et al. Macronutrient intake and depressive symptoms among Japanese male workers: the Furukawa Nutrition and Health Study. Psychiatry Res. 2014; 220(1-2): 263–8. [PubMed: 25200761]
91. Nagata C, Shimizu H, Takami R, Hayashi M, Takeda N, Yasuda K. Serum concentrations of estradiol and dehydroepiandrosterone sulfate and soy product intake in relation to psychologic well-being in peri- and postmenopausal Japanese women. Metabolism. 2000; 49(12):1561–4. [PubMed: 11145117]
92. Nanri A, Kimura Y, Matsushita Y, et al. Dietary patterns and depressive symptoms among Japanese men and women. Eur J Clin Nutr. 2010; 64(8):832–9. [PubMed: 20485303]
93. Nanri A, Shimazu T, Ishihara J, et al. Reproducibility and validity of dietary patterns assessed by a food frequency questionnaire used in the 5-year follow-up survey of the Japan Public Health Center-Based Prospective Study. J Epidemiol. 2012; 22(3):205–15. [PubMed: 22343330]
94. Hirose A, Terauchi M, Akiyoshi M, Owa Y, Kato K, Kubota T. Low-dose isoflavone aglycone alleviates psychological symptoms of menopause in Japanese women: a randomized, double-blind, placebo-controlled study. Arch Gynecol Obstet. 2015

95. Amato P, Young RL, Steinberg FM, et al. Effect of soy isoflavone supplementation on menopausal quality of life. Menopause. 2013; 20(4):443–7. [PubMed: 23211877]

96. Wahner-Roedler DL, Thompson JM, Luedtke CA, et al. Dietary soy supplement on fibromyalgia symptoms: a randomized, double-blind, placebo-controlled, early phase trial. Evid Based Complement Alternat Med. 2011; 2011:350697. [PubMed: 18990724]

97. Jou HJ, Ling PY, Wu SC. Comparison of 70 mg and 35 mg isoflavone soya supplement for menopause symptoms. Int J Gynaecol Obstet. 2005; 90(2):159–60. [PubMed: 15913629]

98. Atteritano M, Mazzaferro S, Bitto A, et al. Genistein effects on quality of life and depression symptoms in osteopenic postmenopausal women: a 2-year randomized, double-blind, controlled study. Osteoporos Int. 2014; 25(3):1123–9. [PubMed: 24114397]

99. Santos-Galduroz RF, Galduroz JC, Facco RL, Hachul H, Tufik S. Effects of isoflavone on the learning and memory of women in menopause: a double-blind placebo-controlled study. Braz J Med Biol Res. 2010; 43(11):1123–6. [PubMed: 20945036]

100. Ishiwata N, Melby MK, Mizuno S, Watanabe S. New equol supplement for relieving menopausal symptoms: randomized, placebo-controlled trial of Japanese women. Menopause. 2009; 16(1): 141–8. [PubMed: 19131846]

101. Mucci M, Carraro C, Mancino P, et al. Soy isoflavones, lactobacilli, Magnolia bark extract, vitamin D3 and calcium. Controlled clinical study in menopause. Minerva Ginecol. 2006; 58(4): 323–34. [PubMed: 16957676]

102. Estrella RE, Landa AI, Lafuente JV, Gargiulo PA. Effects of antidepressants and soybean association in depressive menopausal women. Acta Pol Pharm. 2014; 71(2):323–7. [PubMed: 25272653]

103. Evans M, Elliott JG, Sharma P, Berman R, Guthrie N. The effect of synthetic genistein on menopause symptom management in healthy postmenopausal women: a multi-center, randomized, placebo-controlled study. Maturitas. 2011; 68(2):189–96. [PubMed: 21163595]

104. Chedraui P, San Miguel G, Schwager G. The effect of soy-derived isoflavones over hot flushes, menopausal symptoms and mood in climacteric women with increased body mass index. Gynecol Endocrinol. 2011; 27(5):307–13. [PubMed: 20528204]

105. de Sousa-Munoz RL, Filizola RG. Efficacy of soy isoflavones for depressive symptoms of the climacteric syndrome. Maturitas. 2009; 63(1):89–93. [PubMed: 19339127]

106. Kok L, Kreijkamp-Kaspers S, Grobbee DE, Lampe JW, van der Schouw YT. A randomized, placebo-controlled trial on the effects of soy protein containing isoflavones on quality of life in postmenopausal women. Menopause. 2005; 12(1):56–62. [PubMed: 15668601]

107. Tice JA, Ettinger B, Ensrud K, Wallace R, Blackwell T, Cummings SR. Phytoestrogen supplements for the treatment of hot flashes: the Isoflavone Clover Extract (ICE) Study: a randomized controlled trial. JAMA. 2003; 290(2):207–14. [PubMed: 12851275]

108. Riesco E, Choquette S, Audet M, Tessier D, Dionne IJ. Effect of exercise combined with phytoestrogens on quality of life in postmenopausal women. Climacteric. 2011; 14(5):573–80. [PubMed: 21864137]

109. Lipovac M, Chedraui P, Gruenhut C, Gocan A, Stammler M, Imhof M. Improvement of postmenopausal depressive and anxiety symptoms after treatment with isoflavones derived from red clover extracts. Maturitas. 2010; 65(3):258–61. [PubMed: 19948385]

110. Casini ML, Marelli G, Papaleo E, Ferrari A, D'Ambrosio F, Unfer V. Psychological assessment of the effects of treatment with phytoestrogens on postmenopausal women: a randomized, double-blind, crossover, placebo-controlled study. Fertil Steril. 2006; 85(4):972–8. [PubMed: 16580383]

111. Nikander E, Kilkkinen A, Metsa-Heikkila M, et al. A randomized placebo-controlled crossover trial with phytoestrogens in treatment of menopause in breast cancer patients. Obstet Gynecol. 2003; 101(6):1213–20. [PubMed: 12798527]

112. Albert A, Altabre C, Baro F, et al. Efficacy and safety of a phytoestrogen preparation derived from Glycine max (L.) Merr in climacteric symptomatology: a multicentric, open, prospective and non-randomized trial. Phytomedicine. 2002; 9(2):85–92. [PubMed: 11995954]

113. Song T, Barua K, Buseman G, Murphy PA. Soy isoflavone analysis: quality control and a new internal standard. Am J Clin Nutr. 1998; 68(6 Suppl):1474S–9S. [PubMed: 9848519]

114. Tsunoda N, Pomeroy S, Nestel P. Absorption in humans of isoflavones from soy and red clover is similar. J Nutr. 2002; 132(8):2199–201. [PubMed: 12163662]
115. Ehsanpour S, Salehi K, Zolfaghari B, Bakhtiari S. The effects of red clover on quality of life in post-menopausal women. Iranian journal of nursing and midwifery research. 2012; 17(1):34–40. [PubMed: 23493172]
116. Setchell KD, Clerici C. Equol: history, chemistry, and formation. J Nutr. 2010; 140(7):1355S–62S. [PubMed: 20519412]
117. Ai J, Wang X, Nielsen M. Honokiol and magnolol selectively interact with GABAA receptor subtypes in vitro. Pharmacology. 2001; 63(1):34–41. [PubMed: 11408830]
118. Bharadwaj B, Arasappa R, Venkatasubramanian G, Gangadhar BN. Successful use of adjuvant phytoestrogens in schizoaffective disorder: a case report. Primary care companion to the Journal of clinical psychiatry. 2009; 11(5):268.
119. Stanton R, Reaburn P. Exercise and the treatment of depression: a review of the exercise program variables. J Sci Med Sport. 2014; 17(2):177–82. [PubMed: 23602562]
120. Resnick SM, Maki PM, Rapp SR, et al. Effects of combination estrogen plus progestin hormone treatment on cognition and affect. J Clin Endocrinol Metab. 2006; 91(5):1802–10. [PubMed: 16522699]
121. Resnick SM, Espeland MA, An Y, et al. Effects of conjugated equine estrogens on cognition and affect in postmenopausal women with prior hysterectomy. J Clin Endocrinol Metab. 2009; 94(11):4152–61. [PubMed: 19850684]
122. Schneider LS, Small GW, Clary CM. Estrogen replacement therapy and antidepressant response to sertraline in older depressed women. Am J Geriatr Psychiatry. 2001; 9(4):393–9. [PubMed: 11739065]
123. Regestein QR. Hot flashes, sleep, and mood. Menopause. 2010; 17(1):16–8. [PubMed: 19901855]
124. Cui Y, Niu K, Huang C, et al. Relationship between daily isoflavone intake and sleep in Japanese adults: a cross-sectional study. Nutr J. 2015; 14(1):127. [PubMed: 26715160]
125. Alcantara C, Biggs ML, Davidson KW, et al. Sleep Disturbances and Depression in the Multi-Ethnic Study of Atherosclerosis. Sleep. 2015
126. Schmidt PJ, Nieman L, Danaceau MA, et al. Estrogen replacement in perimenopause-related depression: a preliminary report. Am J Obstet Gynecol. 2000; 183(2):414–20. [PubMed: 10942479]
127. EFSA ANS Panel (EFSA Panel on Food Additives and Nutrient Sources added to Food), 2015. Scientific opinion on the risk assessment for peri- and post-menopausal women taking food supplements containing isolated isoflavones. EFSA J. 2015; 13(10):342. 4246.
128. Vierk KA, Koehler KM, Fein SB, Street DA. Prevalence of self-reported food allergy in American adults and use of food labels. J Allergy Clin Immunol. 2007; 119(6):1504–10. [PubMed: 17451802]

Table 1

Clinical trials evaluating the effects of isoflavones on mental health and depression

Author, year (reference)	Location	Design/ (N)	Intervention Period	Median or Mean Age (y)	Isoflavone dose (mg/d)[1]	Assessment Instrument	Results and Comments	Summary
Hirose, 2015 (94)	Japan	Parallel/(87)	8 weeks	48-51 (38-66% premeno-pausal)	12, 25	HADS[2] AIS[3]	HADS: Isoflavone, -1.15 ± 0.34; Placebo -0.07 ± 0.28* AIS: Isoflavone, -1.82 ± 0.62; Placebo -0.10 ± 0.38** *p=0.033 **p=0.014 Values change from baseline (mean ± SEM) for placebo and 25 mg/d isoflavone group	Isoflavones showed greater benefit than placebo
Estrella, 2014 (102)	Dominican Republic	Parallel/(40)	3 months	45-55	100	HAMD[4] ZSDS[5]	Versus baseline, significant improvement (p<0.001) in all groups for HAMD & ZSRDS. For HAMD, combined group improved (p<0.05) more than other 3 groups. For HAMD, combined group improved (p<0.05) more than soybean and sertraline groups.	Benefit with combination of isoflavones and SSRIs
Atteritano, 2014/(98)	Italy	Parallel/(262)	2 years	49-67	54 Genistein	SF-36[6] ZSDS[5]	Results for the ZSDS | | Genistein | Placebo | | Baseline | 41.00±8.00 | 41.00±7.00 | | Year 1 | 39.00±6.00*,** | 43.00±8.00 | | Year 2 | 36.00±6.00***,**** | 43.00±7.00 | *p <0.05 vs basal; **p <0.05 vs placebo; ***p <0.01 vs basal; ****p <0.01 vs placebo	Benefit compared to baseline and placebo
Amato, 2013/(95)	United States	Parallel/(362)	2 years	40-60	80, 120	MENQOL[7]	| | Placebo | 80 mg | 120 mg | p value* | | Baseline | 2.26 | 2.25 | 2.27 | 0.99 | | 1 year | 2.30 | 2.34 | 2.06 | 0.12 | | 2 year | 1.95 | 1.96 | 1.82 | 0.63 | *Represents one-factor analysis of variance among the three treatment groups. Values are for psychosocial domain	No benefit in response to soy germ-based supplement
Ehsanpour, 2012/(115)	Iran	Parallel/(55)	8 weeks	Isofl. 53.0±3.1 Placebo 53.9±3.2	45	MENQOL[7]	| | Initial | Final | | Isoflavones | 28.11±7.32 | 23.93±7.0* | | Placebo | 26.92±7.33 | 23.67±7.73* | Values are for psychosocial domain. Differences between groups not significant	No benefit
Riesco, 2011/(108)	Canada	Parallel/(40)	6 months	Placebo, 58.3±5.4 Isofl., 60.1±3.4	70	SF-36[6] PSS-10[8]	| | SF-36 | | | Pre | Post | | Ex+Placebo | 49.5 (44.1 – 53.1) | 50.6 (45.9 – 54.5) | | Ex+Isoflavones | 54.1 (49.4–58.9) | 55.7 (54.0 – 57.4) | | | PSS-10 |	No benefit in women engaged in an exercise program

Author, year (reference)	Location	Design/ (N)	Intervention Period	Median or Mean Age (y)	Isoflavone dose (mg/d)[1]	Assessment Instrument	Results and Comments				Summary
							Ex+Placebo	14.6 (12.7 – 17.1)	15.4 (12.0 – 18.8)		
							Ex+Isoflavones	13.3 (10.4 – 16.2)	12.9 (10.6 – 15.1)		
							Values are means (95% CI)				
Evans, 2011/(103)	Canada	Parallel/(82)	12 weeks	40-65	30 Genistein	GCS[9]		Genistein	Placebo	P-value*	No benefit
							Screening	4.60±3 40	4.45±3.48		
							Week 0	4.36±3.19	4.83±3.74		
							Week 4	2.95±3.35	4.19±3.56	0.070	
							Week 8	2.94±2.13	3.62±3.25	0.543	
							Week 12	2.48±2.06	3.35±3.55	0.389	
							% improvemen	t 46	21		
							Values, mean±SD for depression *Diff. between groups				
Chedraui, 2011/(104)	Ecuador	Parallel/(45)	90 days	47.9±4.2	100	HAMD[4]		Baseline	Final	p value*	Benefit vs. baseline
							Means ± SD	16.3±5.4	6.9±5.2	p<0.05	
							% (n) with depressed scores (HAMD ≥ 8)	93.3 (42)	28.9 (13)	p<0.05	
							*Final vs. baseline				
Wahner-Roedler, 2011/(96)	United States	Parallel/(28)	6 weeks	47.7 (range, 18-76)	160 mg	CES-D[10]	Intent-to-treat analysis improvement (%) in scores Soy, 16±26; Placebo, 15±41, p=0.36 Per protocol analysis improvement (%) in scores Soy, 33±30; Placebo, 24±50, p=0.31 50 patients with fibromyalgia enrolled, 28 completers				No benefit
Lipovac, 2010/(109)	Austria	Cross-over/(109)	90 days	53.5±7.1	80	HADS[2] ZSDS[5]		Final			Benefit vs. placebo in anxiety and depression
								Initial	Placebo	Isoflavones	
							HADS				
							Anxiety	9.98±4.68	8.05±4.76	2.40±2.53*	
							Depression	6.91±4.02	5.23±3.65	1.50±2.06*	
							Total	16.89±8.45	13.28±8.00	3.91±4.26*	
							ZSRDS				
							Total	12.24±7.39	9.57±7.01	2.37±3.97*	
							*p<0.001 vs placebo				
Santos-Galduróz, 2010/(99)	Brazil	Parallel/(38)	4 months	Isofl. 54.5±4.3 Placebo 56.6±3.6	80	GDS[11]	Isoflavones	-2.7±5.2			Benefit vs placebo
							Placebo	-5.1±5.9			

Author, year (reference)	Location	Design/ (N)	Intervention Period	Median or Mean Age (y)	Isoflavone dose (mg/d)[1]	Assessment Instrument	Results and Comments				Summary
							Scores represent delta versus baseline, differences not statistically significant				
de Sousa-Munoz, 2009/(105)	Brazil	Parallel/(84)	16 weeks	45-60, Mean, 53.4±3.6	120	CESD[10]		Baseline	Week 8	Week 16	Benefit vs. baseline but not vs. placebo
							Isoflavones	12.5±4.2	9.9±3.6	8.2±3.8[a] (34% ↓)	
							Placebo	13.0±4.8	10.1±4.1	9.4±4. 1[b] (28% ↓)	
							Values are means ± SD				
							[a]p=0.007 wk 16 vs wk 8; p<0.05 wk 16 vs wk 8				
Ishiwata, 2009/(100)	Japan	Parallel/(127)	12 weeks	46.6±3.8	10, 30 equol	Depression (Greene Climacteric Scale) Depression/ Dejection (POMS)[12]		Baseline	Week 12		Benefit for equol non-producers with higher dose
								Equol producers (Depression)			
							Equol-30	1.8±1.0	1.2±1.4		
							Equol-10	0.7± 1.1	0.6±0.7		
							Placebo	1.1±1.3	1.1±1.2		
								Equol producers (Depression/Dejection)			
							Equol-30	48.0±9.2	48.1±6.3		
							Equol-10	46.2±6.2	44.5±3.5		
							Placebo	48.3±5.8	50.1±8.5		
								Equol non-producers (Depression)			
							Equol-30	1.4±1.1	1.0±1.2		
							Equol-10	1.7±1.7	1.2±1.0		
							Placebo	1.7±1.5	1.9±1.1		
								Equol non-producers (Depression/Dejection)			
							Equol-30	48.5±5.6	46.5±4.4*		
							Equol-10	49.4±7.9	48.6±6.7		
							Placebo	51.3±7.6	53.3±9.6		
							P=0.05 vs baseline and placebo final value				
Casini, 2006/(110)	Italy	Cross-over/(76)	6 months	Group A, 49±4.3 Group B, 50±3.9	60	HAMD[4] BDI[13] SSTAI[14] POM[12]		Placebo	Isoflavones	p-value	Benefit vs placebo
							BDI	9.7±6.9	7.6±5.2	0.01	
							POM (depression)	15.3±8.0	10.2±7.8	0.001	
							SSTAI	46.0±9.0	45.0±12	0.40	

Author, year (reference)	Location	Design/ (N)	Intervention Period	Median or Mean Age (y)	Isoflavone dose (mg/d)[1]	Assessment Instrument	Results and Comments					Summary
Mucci, 2006/(101)	Italy	Parallel/(89)	24 weeks	Placebo, 54.4±6.1 Isoflav. 53.3± 5.6	60	Questionnaire	Weeks	4	8	12	24	Benefit vs placebo maintained over 24 weeks
							Isoflavones	-49.1	-69.1	-78.2	-78.2	
							Placebo	-18.2	-30.3	-33.3	-39.4	
							Values represent percent decrease in symptoms; p<0.001 between treatments at weeks 8, 12 and 24					
Kok, 2005/(106)	Netherlands	Parallel/(202)	1 year	60-75	99	SF-36[6] QLSM[15] GDS[11]			Placebo*	Isoflavones*	p-value	No benefit in an older population
							GDS		15	10	0.66	
							QLSM		-3	-3	0.97	
							Satisfaction hormone-specific					
							SF-36 (mental health)		-5	-3	0.26	
							*Values represent % change					
Jou, 2005/(97)	Taiwan	Parallel/(43)	12 weeks	Meno-pausal	35, 70	Not indicated			Initial	4 week	12 weeks	Benefit vs baseline with lower dose of soy germ-derived isoflavones at 12 weeks
							Isoflavones-35		3.5±0.6	2.3±0.4*	1.7±0.5*	
							Isoflavones-70		4.8±0.7	3.8±0.5*	4.3±0.5	
							*p=0.05 vs baseline (differences between groups not significant)					
Nikander, 2003/(111)	Finland	Cross-over/(56)	3 months	54±6 (35-69)	114	13 questions[16]	Depression index	Before	After			Both soy germ-derived isoflavone and placebo groups improved
							Placebo	5.7±4.5	4.4±4.2			
							Isoflavones	6.1±5.0	4.6±4.4			
							Values are mean ± SD. Difference between groups, p=0.663Scores 5–7 = mild depression; 8-15, moderate depression; and >16=severe depression. Participants had breast cancer					
Tice, 2003/(107)	United States	Parallel/(246)	12 weeks	52.3± ~3.0	82, 57.2	GCS[9]	Promensil* (isoflavones)		Rimostil ** (isoflavones)		Placebo	No benefit
							-0.7 (-1.1, 2.0)		-0.4 (-0.8, -0.2)		-0.3 (-0.7, -0.2)	
							*vs. placebo, p=0.23 **vs placebo, p=0.79 Scores, mean (95% CI) CGS depression subscale					
Albert, 2002/(112)	Spain	Open/(190)	4 months	>45	35	Question- naire	Baseline	2 months		4 months		Benefit vs. baseline in response to soy-germ derived isoflavones
							49.86±30.67	36.80 ± 27.68		28.83 ± 27.89		
							p=0.03 baseline vs 4 mo					

[1] Expressed as aglycone equivalent weight

[2] HADS, The Hospital Anxiety and Depression

[3] AIS, Athens Insomnia Scale

[4] HAMD, Hamilton Rating Scale for Depression

[5] ZRDS, Zung's Self Rating Depression Scale

[6] SF-36, Short Form-36

[7] MENQOL, Menopause-Specific Quality of Life questionnaire

[8] PSS-10, Perceived Stress Scale-10 questionnaires

[9] Green Climatic Scale

[10] CESD, Depressive symptoms of the Center of Epidemiologic Studies of Depression

[11] GDS, Geriatric Depression Scale

[12] POM, Profile of Mood States

[13] BDI, Beck Depression Inventory (BDI)

[14] SSTAI, Spielberger State-Trait Anxiety Inventory

[15] QLSM, Questionnaire on Life Satisfaction Modules

[16] 13 questions concerning mood, social behavior, and opinion of the future