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Soy and Red Clover for Midlife and Aging

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Abstract

Introduction— Menopause is associated with midlife, a time when many women begin to experience the signs and symptoms of aging, such as increases in blood pressure, changes in lipid profiles, loss of bone mass density, and diminished memory and cognition. Given the result of the Women's Health Initiative, many women no longer consider hormone therapy the first option for promoting healthy aging. Instead they are turning to botanical and dietary supplement (BDS) products in place of hormone therapy. This paper reviews the evidence available for use of isoflavones from soy and red clover, for the treatment or prevention of these health issues.

Methods— The MEDLINE and EMBASE databases was searched for articles relating to soy or red clover supplement use for prevention and/or treatment of heart disease, hyperlipidemia, osteoporosis, mood disorders and cognitive abilities. Studies were included if they were randomized, controlled trials and included peri- or postmenopausal women.

Results— Isoflavone products appear to be the most useful for improving lipid profiles; however, the evidence suggests that isoflavone extracts from soy are less effective than products containing soy protein or red clover isoflavones. Soy protein appears to reduce total cholesterol levels and LDL cholesterol, while red clover reduces triglycerides and increases HDL cholesterol. The data was somewhat less convincing, although promising, for increasing bone mass density and improving cognitive abilities.

Conclusions— Research suggests that isoflavone found in soy foods and red clover appear to have a small but positive health effect on plasma lipid concentrations, bone mass density, cognitive abilities. Given the lack of serious safety concerns in the short term, it would appear that including soy and red clover in the diet of postmenopausal women, not withstanding a soy allergy, would be beneficial.

Keywords

isoflavones; soy; red clover; lipids; bone mass density

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Introduction

Although many women experience symptoms during the menopausal transition, 25–30% of women have relatively few if any bothersome complaints.[1] Menopause, however, is associated with midlife, a time when many women begin to experience the signs and symptoms of aging, such as changes in lipid profiles, increases in blood pressure, increased vulnerability to heart disease, loss of bone mass density, increased fracture risk, and diminished memory and cognitive abilities. Although hormone therapy is still considered the first line of treatment for vasomotor symptoms, given the results of the Women's Health Initiative, it is neither considered by providers nor desired by patients as the first line of treatment or prevention for conditions related to aging.[2] Rather, many women are turning to botanical and dietary supplement (BDS) products for prevention or treatment of these health issues.

In many countries of the world, botanicals are not well regulated by federal or governmental agencies. For example, in the US, botanicals are overseen according to the Dietary Supplement Health Education Act (DSHEA). DSHEA classifies botanicals as dietary supplements, not drugs, which are not intended for diagnosis, prevention, or treatment and therefore are not subject to regulation by the Federal Drug Administration (FDA). This lack of regulatory oversight has resulted in considerable variability of content, standardization, dosage, and purity of available products in the US. The European Food Safety Authority has only recently begun to address the issue of botanical safety and purity regulation for its member states.[3] By contrast, dietary supplements have been scrutinized for safety and efficacy by the Commission E in Germany for two decades.[4]

Despite the lack of regulation, the use of BDS among menopausal women has increased exponentially in recent years across the developed world.[5–7] In studies performed in the United Kingdom and US most women report using these products because they find alternative therapies more congruent with their values and lifestyles.[7, 8] However, few women understand the health benefits and risks of these supplements and consequently do not inform their health care providers about use of these products.[9] Compounding this problem is that many conventional practitioners are not trained in use of BDS and do not ask their patients about use of these alternative treatments.[10–12]

Dietary supplements with isoflavones from either soy or red clover have been two of the most commonly utilized botanicals for peri- and postmenopausal women. Soy foods and supplements as well as red clover have been the subject of much interest for the reduction of menopausal symptoms and conditions related to aging because of their high concentrations of phytoestrogens, specifically isoflavones which are thought to be especially healthful. Soy and red clover share similar but distinct chemical profiles: both contain genistein, daidzein, formononetin, and biochanin A, but red clover has significantly higher levels of the *O*-methylated isoflavones, formononetin and biochanin A, while soy has higher levels of daidzein and genistein.[13, 14]

The studies of soy and red clover as a plant/food for alleviation of menopausal symptoms have not provided a clear answer to their role in reducing menopausal symptoms. A review of the literature from the more rigorous trials shows, at best, only a modest effect on vasomotor symptoms.[15–17] However, many women continue to use isoflavones from soy and red clover as they age and careful examination of the safety and efficacy of these products for prevention and treatment of health conditions beyond that of menopause must be carefully considered. This paper reviews the scientific literature on efficacy and safety of soy and red clover for hyperlipidemia, osteoporosis, mood and cognition.

Methods

Articles relating to soy or red clover supplement use for prevention and/or treatment of heart disease, hyperlipidemia, osteoporosis, mood changes and cognitive abilities were found by searching the MEDLINE and EMBASE databases from 1966 to July 2005. Terms used in the search strategy included: soy foods, soy isoflavones, isoflavones, red clover, trifolium, lipids, hyperlipidemia, heart disease, osteoporosis, bone mass, bone mineral density, bone loss, bone mineral content, memory, mood, and cognition. Abstracts of all articles were reviewed for inclusion in the study, and the bibliographies of reviews were searched for relevant articles. If articles met inclusion criteria, the entire article was reviewed by the authors.

Studies were eligible for inclusion if study subjects included peri- or postmenopausal women, studies were designed as randomized, controlled trials, and the outcome reported on included heart disease, lipid profiles, bone loss, bone mineral density, bone mineral content, memory, or cognitive function. Studies that did not include peri- or postmenopausal women as subjects or were not randomized, controlled trials were excluded. Doses and types of soy supplementation as well as dose of red clover isoflavone varied among studies, and details on each trial are outlined in the accompanying tables. Because soy and red clover have similar yet distinct profiles each is discussed separately.

Results

Heart disease/hyperlipidemia

Heart disease is a leading cause of death for women throughout the world in both developed and developing nations.[18, 19] For example, in the US over 8,000,000 women are currently living with heart disease and approximately 10% of these women are between the ages of 45–64. It is after menopause that a woman's risk of heart disease begins to increase and one of the major risk factors for heart disease is elevated cholesterol levels.[19] Several studies have examined the effects of soy and red clover on reducing overall cholesterol, lowering low density lipoproteins (LDL) and triglycerides, and raising high density lipoproteins (HDL). These studies are detailed inTables 1 and2 and summarized below.

Soy—Soy is one of the most commonly utilized dietary supplements or functional foods used by menopausal women.[9, 47] Several studies have demonstrated that soy may be effective in reducing serum lipid levels for both men and women. A meta-analysis of 38 controlled human studies (including both men and women) of soy consumption found that individuals who replaced animal protein with soy protein had a significant decrease in overall cholesterol and LDL cholesterol concentrations compared to those who consumed protein from animal sources.[48] Subjects with higher initial serum cholesterol concentrations had a greater absolute and percent change in cholesterol levels compared to people with lower initial cholesterol. The US FDA approved a health claim for isoflavone rich soy protein stating that consumption of 25g of soy protein daily can reduce cholesterol.[49] The German Commission E has also approved soy (as soy lecithin or soy phospholipid) for hypercholesterolemia.[4]

There have been 21 randomized, controlled trials of soy foods, soy supplements, or soy isoflavone supplements for lipid changes in peri- and postmenopausal women. Type of soy supplementation varied widely among studies—18 trials used soy food or isolated soy protein (ISP), and 3 used phytoestrogen tablets or extracts. In clinical trials that used soy food or ISP supplement, half of the studies found a significant lipid lowering effect of soy compared to placebo (9 of 18 trials). [20–26, 28, 29] Of these, five found a change in the LDL:HDL ratio with decreases ranging from 5–11%,[20–21, 23–24, 26] three studies found decreases in LDL cholesterol ranging from 6 to 15%,[20, 24, 25] but only one study found a significant increase in HDL cholesterol.[22]

The remaining nine trials of ISP and placebo (usually casein protein) found no changes in cholesterol due to soy [27, 30–37] and 3 RCTs using a phytoestrogen tablet derived from soy found no significant differences in lipid levels compared to placebo.[38–40] Thus far, the available data suggests that products containing soy protein, not only isoflavone supplements, may be useful for reducing serum cholesterol levels in postmenopausal women.

Furthermore, some studies of soy to lower blood cholesterol have shown that use of soy is more likely to be efficacious in equol producers.[50] Equol is a nonsteroidal estrogen that is the product of intestinal bacterial metabolism of dietary daidzen (an isoflavone) commonly found in soy foods. Between 30–50% of adults do not produce equol when eating soy foods regularly.[50] Most of the studies reviewed above did not examine if the subjects were equol producers; it is possible that the variation in the efficacy of soy to reduce cholesterol is attributable to this variation in equol production.

Red Clover—Since red clover contains isoflavones similar to soy, researchers have hypothesized that it would also positively affect lipid profiles. There have been six RCTs of red clover isoflavones in peri- and postmenopausal women, and five of the six studies found some positive effect of red clover isoflavones on lipids. None of the studies reported a significant change in total cholesterol or LDL cholesterol. However, two of the trials found that HDL was significantly increased compared to placebo, two found non-significant trends of increase in HDL over time, and 2 found significant decreases in triglycerides. [41–46]

Red clover contains higher concentration of formononetin and biochanin A and lower concentrations of daidzen and genistein than soy, suggesting that an individual's equol production status may be less relevant. The results of the reviewed trials suggest that red clover has a different mechanism of action than soy isoflavones, which would be consistent with its different isoflavone makeup. Soy appears to reduce total cholesterol levels and LDL cholesterol, while red clover reduces triglycerides and increases HDL cholesterol.

Osteoporosis

The incidence of osteoporosis is increasing worldwide as populations age and women are four times more likely than men to develop osteoporosis.[51] By year 2010, 35 million women in the US alone will either have osteoporosis or be at risk of developing this condition.[52] In the UK, over three million people, predominantly women, suffer from osteoporosis, with over 200,000 fractures a year occurring as a result.[53] Bone loss is most rapid in the first few years after menopause but may persist into the postmenopausal years. Because of their selective estrogenic like activity, soy and red clover have been hypothesized to have a positive effect on bone mineral density as women age (Tables 3 and4).

Studies of isoflavones for osteoporosis prevention typically have used either bone mineral content (BMC), bone mineral density (BMD), or markers of bone resorption as outcomes rather than incidence of hip fracture. Both BMC and BMD are measured using dual-energy x-ray absorptiometry (DEXA).[1] Bone resorption markers measure molecules associated with bone turn over and loss.

Soy—Data from several observational studies have suggested that populations with a high mean intake of soy, such as Japan, have a lower incidence of osteoporotic fractures compared to Western populations.[63, 64] However, when these comparisons are made between populations, numerous confounders such as amount and type of soy consumption, amount and

[1]BMC is the mg of mineral in the bone. BMD is mg of mineral per centimeter squared; therefore BMD is equal to BMC divided by surface area of bone tested.

type of physical activity, and other lifestyle factors limit the results.[65] Animal studies show consistent bone conserving effects or improvement in BMD, while human studies have shown at best modest gains in BMD and BMC.

Fourteen randomized controlled trials have been conducted to examine the effects of soy on bone mineral density in peri- and postmenopausal women (Table 3). The majority of these studies used BMD or BMC as the main outcome measure, while three studies examined markers of bone resorption. Seven studies found that BMD or BMC was significantly higher after supplementation with isoflavone tablet, ISP, or soy foods, compared to placebo.[22, 54–59] Bone density was either higher because it increased in the soy groups and stayed the same in the placebo groups or because BMD stayed the same in the soy groups and decreased in the placebo groups.

One study conducted in Chinese women found that isoflavones produced a greater rate of increase in BMC for women who began with lower bone mass.[59] They also found the rate of change in BMC was affected by a longer time since menopause, lower body weight, and lower mean calcium intake.[60] Only one of the three studies that measured bone resorption markers demonstrated a significant difference between isoflavone capsule and control.[40]

Because there has not been consistent data to show that soy isoflavones protect against or lessen bone loss, some authors have put forward explanations for the differential results. In a review by Weaver and Cheong,[67] the authors suggest four explanations for a lack of consistent effect of soy. First, soy's effect on bone could be life-stage or estrogen dependent, meaning that it is only effective during times of estrogen deficiency such as peri- and post menopause. This hypothesis is consistent with some of the data reviewed for this paper. The majority of the studies conducted on post menopausal women (9 of 14 reviewed) demonstrated that soy/isoflavones protect against bone loss.

A second explanation is that the bone-protective effects of soy could be due to only one type of isoflavone, and when these compounds are found in combination, they may have opposing effects. All but one of the studies reviewed for this paper used whole soy or combinations of isoflavones. The one study that examined genistein alone found increased BMD in femur and lumbar spine,[55] although the seven studies which used soy or combinations of isoflavones also showed improvement in BMD.[22, 40, 54, 56–59]

Third, some authors have found that soy has a positive effect on bone in equol producers but not in non-producers. Only one study reviewed for this paper examined equol status of the participants and found no difference in soy's effectiveness between equol producers and non-producers.[36] Finally, soy studies in general may have poor dietary control for other factors that effect bone loss. The dietary control of the studies reviewed for this paper was mixed, with only 2 studies using controlled feeding or special diets.[22, 65] Most studies merely added supplements to the usual diet so the impact of other calcium rich or calcium depleting foods is unclear. The fact that most trials do not control for concomitant dietary modifications poses a serious limitation for studies of both soy and red clover.

Red Clover—The bone preserving effects of red clover have also been examined, but not as extensively as that of soy. Only three randomized controlled trials of red clover isoflavones for bone loss have been published (Table 4). Two of the trials demonstrated a positive effect of red clover on bone mineral density[42, 45] as well as an increase in bone formation markers.[45] A third study examined bone resorption markers and found no effect.[43] Although the evidence is very limited, it appears that red clover isoflavones may have a somewhat helpful effect on bone mineral density in peri- and postmenopausal women.

Cognition

Cognitive problems and forgetfulness are common complaints for peri- and post menopausal women.[68] Few studies have been published examining the relationship between isoflavones found in soy or red clover on cognitive function in postmenopausal women. Three of the four studies of soy or soy isoflavones for cognition found a positive effect (Table 5).[69–71] All three used isoflavone tablets, but the one study[34] which showed no effect used ISP. The three positive studies found improvements in short-term memory, frontal lobe function, mental flexibility, planning ability, category fluency, and sustained attention.[69–71] The only study of red clover isoflavones for cognitive function found no difference between treatment and control groups.[46] It appears that soy isoflavones could have positive effects on cognitive function in postmenopausal women; however, more research is needed for both soy and red clover isoflavones.

Safety

Overall, isoflavones from both soy and red clover have positive safety profiles. Only a few of the trials reviewed for this paper reported safety outcomes beyond mild side effects. The most commonly reported side effects of soy are gastrointestinal complaints such as stomach pain, loose stool, and diarrhea.[4] Soy should be avoided if an allergy exists. The side effects reported for red clover are mild and include headache, myalgia, and nausea. Several other studies have reported on the safety of soy and red clover.

In most short term studies of 3–6 months, soy has not been found to increase the risk of endometrial cancer or endometrial hyperplasia, with one study showing a higher intake of soy isoflavones linked to a decreased risk of endometrial cancer. [72,73] However, one long-term 5 year trial of the effects of soy isoflavone on endometrial tissue found a significantly increased incidence of endometrial hyperplasia in the group taking soy isoflavone. The increased incidence was small (3.7% vs. 0%), and no cases of endometrial cases were reported.[74] Red clover also has a positive safety profile and appears not to negatively affect the endometrium, [75] although there have been very few studies that specifically looked at the effects of red clover on the endometrium.

Soy and red clover have been studied both *in vitro* and in animal models to examine the risk of breast cancer. *In vitro* studies of both soy and red clover show that they do not promote breast cell proliferation.[76–78] A comprehensive review of animal studies provide compelling evidence of 25–50% fewer tumors in animals consuming soy protein compared to controls consuming other protein sources.[79] Studies of purified isoflavones have been mixed with some showing cancer protective effects and one showing increased tumorgenesis.[80, 81]

Human studies show no negative effect on the breast and some have suggested a protective effect of soy on breast tissue. Several case-control studies in Asian countries have demonstrated decreased rates of breast cancer.[66–68] It is interesting to note, however, that when Japanese women move to the US, the cancer risk has increased. The presumed protective effect of soy isoflavones may have been a combination of several factors including the consumption of soy early in life, a low fat and high fiber diet, as well as a less sedentary lifestyle.

Some research has suggested that there may be different mechanisms of action for soy/red clover in the presence or absence of estradiol. In the absence of estradiol, isoflavones might exhibit estrogen-agonistic activities, while in the presence of estradiol, soy/red clover may exhibit antagonistic effects which has induced cell proliferation. This hypothesis suggests that different treatment strategy for peri-menopausal women (with higher levels of estradiol) and postmenopausal women (with lower levels of estradiol) may be necessary.[82]

Conclusions

Isoflavone extracts of soy and red clover appear to have a small but positive health effect for plasma lipid concentrations and may improve bone mass density and cognitive abilities. However, the positive effects on coronary disease, bone, and cognition are small and need to be further studied to assess the clinical significance of these findings. Isoflavones have shown their greatest effect for lowering lipids although the effects appear to be limited to products containing soy protein, not only extracted isoflavones. Their use may ultimately result in a reduced risk of heart disease for women, although this important outcome of interest has not been studied. The evidence has been somewhat less convincing, although promising, regarding the use of soy isoflavones for increasing bone mass and improving cognition. Again, reduction in fracture rates should be studied as the outcome of importance as well as the possible long term effect on decreasing risk for dementia.

There is at this time no consensus as to the appropriate recommended dose of isoflavones for any of these health conditions; however, daily doses in the amount of 80–120 milligrams appear to have the greatest effect with a positive safety profile. Given the lack of serious safety concerns in the short term, it would appear that including soy and red clover in the diet of peri- and postmenopausal women, not withstanding a soy allergy, is beneficial. Of course, longer term safety studies are needed.

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Table 1

Randomized, Controlled Trials of Soy for Lipids in postmenopausal women

First author, year	*Design*	*Subjects*	*Intervention type, dose, and duration*	*Outcome*
Dalais, 2003 [20]	RCT with 2 groups: ISP or casein placebo supplement	• Postmenopausal women • Ages 50–75 • n=106	ISP contained 40 g/day of soy protein and 118 mg isoflavones. **Duration:** 3 months	Significant decreases in LDL, triglycerides, and LDL/HDL ratio in soy group compared to placebo.
Jenkins, 2002 [21]	RCT with crossover design. 3 one-month phases separated by a 2 week wash-out period. Phases: dairy food diet (control), low-isoflavone soy diet, high-isoflavone soy diet.	• Men and postmenopausal women • Hyperlipidemic • Mean age=62 (men and women) • n=41 (18 women)	In all 3 phases, subjects followed the NCEP Step II diet & substituted low fat dairy or soy foods for dietary protein sources. Dairy and soy foods were provided to participants. Low isoflavone: 10 mg/day High isoflavone: 73 mg/day **Duration:** 1 month each diet.	Significant difference between control phase diet and both soy diets in total cholesterol, total/HDL cholesterol ratio, LDL/HDL ratio.
Potter, 1998 [22]	RCT with 3 groups: ISP low isoflavones, ISP high isoflavones, or casein placebo	• Postmenopausal women • Hypercholesterolemic • Ages 39–83 • n=66	Both ISP supplements contained 40g/day soy protein. Low isoflavone: 56 mg/day. High isoflavone: 90 mg/day. Background diet: NCEP Step I diet. **Duration:** 6 months	Significant decreases in non-HDL cholesterol for both soy groups compared to placebo. Significant increase in HDL cholesterol for both soy groups compared to placebo.
Vigna, 2000 [23]	RCT with 2 groups: ISP or casein placebo	• Postmenopausal women • Mean age=53 • n=104	ISP contained 60g/day of soy protein **Duration:** 12 weeks	Significant reduction in LDL/HDL ratio in soy group compared to placebo. Dislipidemic women at baseline, significant reduction in LDL with soy.
Wangen, 2001 [24]	RCT with crossover design. Three 93 day periods subjects consumed ISP with 3 different amounts of isoflavones. 26 day washout between each intervention	• Postmenopausal women • Ages 40–70 • n=18	ISP supplement levels of isoflavone were 7.7 mg/day (control), 65 mg/day (low), and 132 mg/day (high). Background diet did not change. **Duration:** 93 days each intervention	LDL cholesterol 6.5% lower after high isoflavone phase. LDL/HDL ratio 8.5% lower after low isoflavone phase and 7.7% lower after high isoflavone phase.
Washburn, 1999 [25]	RCT with crossover design. 3 supplements: Control, low isoflavone, high isoflavone.	• Perimenopausal women • Median age=51 • n=51	Control diet: complex carbohydrates Low isoflavone: 34mg/day High isoflavone: 68 mg/day **Duration:** 6 weeks each supplement	Significant decline in total cholesterol and LDL cholesterol in both soy supplements compared to control supplement.
Teede, 2001 [26]	RCT with 2 groups: Isolated soy protein (ISP) or casein placebo supplements	• Men and postmenopausal women • Ages 50–75 • n=213 (105 women)	Soy supplement contained 40g/day soy protein and 118 mg/day isoflavones. Supplements were in powdered form. Background diet did not change in either group. **Duration:** 3 months	Significant reduction in LDL/HDL ratio and triglycerides in soy group compared to placebo.
Chiechi, 2002 [27]	Randomized, controlled trial (RCT) with 3 groups: Soy-rich diet, HRT group, control group.	• Healthy peri and postmenopausal women • Ages 39–60 • n=187	Soy-rich diet group added 1 soy food serving per day and exchanged 2 meals 2 times a week with soy	Decrease in non-HDL cholesterol in HRT and diet groups higher than in the control group, but not statistically significant.

First author, year	*Design*	*Subjects*	*Intervention type, dose, and duration*	*Outcome*
			rich meals provided by the study. **Duration:** 6 months	Study hampered by low compliance in the diet group (>50% dropped out) **Safety:** endometrial thickness increased slightly in soy diet group, increased significantly in HRT group.
Engleman, 2005 [28]	RCT with 4 groups: ISP with (a) low phytate/low isoflavone (LPLI), (b) normal phytate/ low isoflavone (NPLI), (c) low phytate/normal isoflavone (LPNI), (d) normal phytate/ normal isoflavone (NPNI)	• Postmenopausal women • Ages 47–72 • n=55	All ISP supplements contained 40 g of soy protein. Normal background diet Low phytate: 0.22g Normal phytate: 0.64g Low isoflavone: 1.2 mg Normal isoflavone: 86 mg **Duration:** 6 weeks	Both total and LDL cholesterol decreased from baseline in all groups, but no significant differences were found between treatment groups.
Mackey, 2000 [29]	RCT with 2 groups: ISP with or without isoflavones.	• Postmenopausal women • Hyperlipidemic • Ages 45–65 • n=54	Both ISP supplements contained 28g/day soy protein, With isoflavone 65 mg/day No isoflavone <4mg/ day. Background diet National Heart Foundation guidelines (Australia). **Duration:** 12 weeks.	Both groups had a significant reduction in total cholesterol and LDL cholesterol. There were no significant differences between groups.
Blum, 2003 [30]	RCT with crossover design. ISP or casein protein. Washout period 4 weeks	• Postmenopausal women • Hypercholesteremic • Mean age=55 • n=24	ISP contained 25g/day of soy protein and 85 mg/day isoflavones. Usual background diet. **Duration:** 6 weeks each treatment	Triglycerides increased and total cholesterol and LDL decreased significantly compared to baseline. There were no differences between the groups.
Cuevas, 2003 [31]	RCT with crossover design. ISP and casein protein supplements	• Postmenopausal women • Hypercholesteremic • Ages 47–70 • n=18	ISP contained 40g/day soy protein and 80mg/ day isoflavones. Background diet was NCEP Step I diet. **Duration:** 4 weeks each treatment, no washout	Total and LDL cholesterol levels lower for both treatments compared to baseline. There was no difference between soy or milk protein.
Dent, 2001 [32]	RCT with 3 groups: ISP with and without isoflavones, whey protein.	• Perimenopausal women • Normal and mildly hypercholesteremic • Ages 42–62 • n=69	ISP with isoflavones: 80 mg/day ISP no isoflavones: 4 mg/day ISP and whey total of 40g of protein a day. **Duration:** 24 weeks	There were no differences between ISP (+), ISP (−), and control in total cholesterol, triglycerides, LDL or HDL.
Gardner, 2001 [33]	RCT with 3 treatment groups: ISP with (+) and without (−) isoflavones, casein protein.	• Postmenopausal women • Hypercholesteremic • Mean age 51–62 • n=94	ISP with isoflavones: 80 mg/day ISP no isoflavones: contained trace amounts isoflavones. ISP and casein total of 40g of protein a day. **Duration**: 4 week run in and 12 week treatment	LDL decreased more in ISP (+) group than ISP (−) group, but neither significantly different from casein group. No significant differences between groups for triglycerides and HDL cholesterol.
Kreijkamp-Kaspers, 2004 [34]	RCT with 2 groups: ISP or casein protein	• Postmenopausal women • Ages 60–75 • n=202	ISP contained 25.6 g/ day of soy protein and 99mg/day of isoflavones. **Duration:** 12 months	No significant differences in LDL or total cholesterol after one year.
West, 2005 [35]	RCT with crossover. 2 diets: ISP or casein protein	• Postmenopausal women, 2 groups, taking HT (HT +), not taking HT (HT−) • Hypercholesterolemic	ISP and casein contained 25g/day of protein, ISP had 90mg/ day of isoflavone.	In HT(−) women, significant reductions in LDL, HDL, and triglycerides during the Step I diet only phase. Soy

First author, year	*Design*	*Subjects*	*Intervention type, dose, and duration*	*Outcome*
		• Mean age: • HT+ = 57.2 • HT− = 59.2 • n=18 women • HT− = 12	Background diet was NCEP Step I diet. All food provided by study. **Duration:** 3 week run-in of Step I diet, 6 weeks treatment with supplement.	or milk protein had no additional effect. For HT (+) women, triglycerides reduced by the Step I diet, no additional changes of soy or casein protein.
Gallagher, 2004 [36]	RCT with 3 groups: ISP with high, low, or no isoflavone	• Postmenopausal women • Mean age=55 • N=65	High isoflavone 96mg/d Low isoflavone 52 mg/d No isoflavone <4mg/d **Duration:** 9 months	No effect of any of the ISP supplements on lipid measurements between the groups.
Roughead, 2005 [37]	Controlled feeding study with crossover design. 2 groups: control diet and soy diet	• Postmenopausal women • Ages 52–69 • N=13	In soy diet, 25g high-isoflavone soy protein was substituted for an equivalent amount of meat protein. **Duration:** 7 weeks each diet	Diet did not effect lipid profile.
Dewell, 2002 [38]	RCT with 2 groups: placebo or phytoestrogens supplement	• Postmenopausal women • Hypercholesterolemic • Mean age=69 • n=36	Phytoestrogen supplement in form of a pill. Total of 150 mg/day. **Duration:** 6 months	No significant differences between groups in total cholesterol or triglycerides.
Simons, 2000 [39]	RCT with crossover design. Placebo and Soy phytoestrogens tablet intervention	• Postmenopausal women • Ages 50–70 • n=20	Soy phytoestrogens total of 80 mg/day of isoflavones. Background diet fat restricted. **Duration:** 8 weeks each treatment with washout	LDL and HDL significantly lower after treatment in both placebo and phytoestrogens groups compared to baseline. **Safety:** no significant changes in routine biochemistry, liver function, or hematology.
Uesugi, 2002 [40]	RCT with 2 groups: soy isoflavone capsule and placebo	• Perimenopausal women • Ages 40–62 • N=23	Soy isoflavone capsule contained 61.8 mg of isoflavones. **Duration:** 4 weeks	LDL and total cholesterol fell significantly from baseline in isoflavone group, but not significantly different from placebo after intervention.

* Abbreviations: RCT=Randomized Controlled Trial, ISP=Isolated Soy Protein, NCEP=National Cholesterol Education Program, HT=hormone therapy

Table 2

Randomized, Controlled Trials of Red Clover for Lipids in postmenopausal women

Author, year	*Design*	*Subjects*	*Intervention type, dose, and duration*	*Outcome*
Campbell, 2004 [41]	RCT with crossover. 2 interventions were placebo and Promensil®.	• Pre and postmenopausal women • Mean age=57 (postmenopausal women) • n=7 (postmenopausal women)	Women took two tablets each day of Promensil. **Duration:** 1 month	postmenopausal women only Total cholesterol and triglycerides not affected by treatment. HDL concentrations were significantly elevated over placebo.
Clifton-Bligh, 2001 [42]	RCT with 3 groups. One month of placebo period followed by 6 months of treatment and 1 month of placebo washout. Placebo periods were single blinded.	• Postmenopausal women • Mean age range 55–59 • n=46	The three doses of Rimostil were: 28 mg/d, 57 mg/d, and 85.5 mg/d of isoflavones. **Duration:** 6 months	Serum HDL rose significantly with all three doses, but no dose-response effect. **Safety:** endometrial thickness did not change significantly during treatment.
Schult, 2004 [43]	RCT with 3 groups: Promensil®, Rimostil®, and placebo	• Perimenopausal women • Ages 45–60 • n=250	Promensil: Red clover extract with 41 mg isoflavones per tablet Rimostil: Red clover extract with 28.6 mg isoflavones per tablet. Two tablets per day of each treatment. **Duration:** 12 weeks	Both extracts showed a significant decrease in triglyceride levels compared to placebo--decrease mainly among women with elevated triglycerides at baseline. Both extracts showed higher increases in HDL cholesterol compared placebo--increase of small magnitude and not significant.
Nestel, 1999 [44]	RCT with 2 groups: placebo or increasing does of isoflavone	• Postmeneopausal women • Ages 41–71 • N=17	Promensil containing 40g of isoflavone was used. Active therapy group took 1 tablet Promensil for 5 weeks, then 2 tablets for another 5 weeks. **Duration:** 10 weeks total	No significant differences in plasma lipids with treatment. Over time a downward trend in LDL and an upward trend in HDL, reducing the LDL/HDL ratio by 10% in treatment vs. control (not statistically significant).
Atkinson, 2004 [45]	RCT with 2 groups: Placebo or isoflavone tablet	• Pre, peri, and postmenopausal women • Ages 49–65 • N=205	Promensil tablet was uses as treatment. One tablet per day in intervention group. **Duration:** 12 months	No significant differences overall in total cholesterol, LDL, triglycerides, or HDL between treatments. Significant interaction between treatment and menopausal status for triglycerides only. Perimenopausal women taking isoflavone experienced a significant decrease in plasma triglycerides.
Howes, 2000 [46]	RCT with 2 groups placebo or increasing doses of isoflavone. Active: control group ratio of 6:1	• Postmenopausal women • Hypercholesterolemic • Mean age=58.3 • N=75	One isoflavone tablet contained 26 mg biochanin A, 16 mg formononetin, 0.5 mg daidzein, and 1mg genistein. Isoflavones were extracted from red clover. Active therapy group took 1 tablet for 5 weeks, then 2 tablets for an additional 5 weeks **Duration:** 10 weeks total	In both the active and control groups, no significant changes in total cholesterol, triglycerides, HDL, or LDL cholesterol.

* Abbreviations: RCT=Randomized Controlled Trial

Table 3

Randomized, Controlled Trials of Soy for Bone in postmenopausal women

Author, year	*Design*	*Subjects*	*Intervention type, dose, and duration*	*Outcome*
Potter, 1998 [22]	RCT with 3 groups: ISP low isoflavones, ISP high isoflavones, or casein placebo	• Postmenopausal women • Ages 39–83 • n=66	Both ISP supplements contained 40g/day soy protein. Low isoflavone:56 mg/day. High isoflavone: 90 mg/day. Background diet NCEP Step 1 diet. **Duration:** 6 months	Significant increases in BMC and BMD occurred in lumbar spine for high isoflavone group compared to placebo.
Harkness, 2004 [54]	RCT with cross-over design placebo and soy isoflavone capsule	• Postmenopausal women • Mean age 70.6 • N=19	Soy isoflavone capsule contained 110 mg/day isoflavones (1.3:1.0:0.2 ratio of genistein: daidzein: glycitein) **Duration:** 6 months	Mean spine BMD significantly greater in treatment compared to control.
Morabito, 2002 [55]	RCT with 3 groups: HT, genistein, and placebo	• Postmenopausal women • Ages 47–57 • N=90	HT: 1 mg 17β-estradiol and 0.5 mg norethisterone acetate. Genistein: 54 mg/day **Duration:** 1 year	Both genistein and HT significantly increased BMD in the femur and lumbar spine.
Alekel, 2000 [56]	RCT with 3 groups: ISP with isoflavones (ISP+), ISP without isoflavones (ISP−), and control	• Perimenopausal women • Median age=50 • N=69	ISP+ contained 80mg/day isoflavones. Both ISP+ and ISP− contained 40g/day of soy protein. **Duration:** 24 weeks	Regression analysis showed that ISP+ treatment had a positive effect on change in BMD.
Lydeking-Olsen,2004 [57]	RCT with 4 groups: soymilk, transdermal progesterone, combination, and placebo	• Postmenopausal women • Caucasian • With established osteoporosis or 3 risk factors for the disease • N=89	Soymilk contained isoflavones. Combination group consumed soymilk and used transdermal progesterone. Placebo group consumed isoflavone-free soymilk and progesterone-free cream. **Duration:** 2 years	In the soymilk group, BMC and BMD did not differ from baseline, but significant bone loss occurred in placebo group and combination group.
Chiechi, 2002 [58]	RCT with 3 groups: Soy-rich diet, HT group, control group.	• Healthy postmenopausal women • Ages 39–60 • n=187	Soy-rich diet group added 1 soy food serving per day and exchanged 2 meals 2 times a week with soy rich meals provided by the study. **Duration:** 6 months	Diet not as effective as HT in reducing bone turnover. BMD significantly decreased only in the control group. **Safety:** endometrial thickness increased slightly in soy diet group, increased significantly in HT group.
Chen YM, 2003 [59]	RCT with 3 groups: placebo, mid-dose, and high-dose, in pill form	• Postmenopausal women • Chinese • Ages 48–62 • N=203	All supplements contained 500mg/d calcium and 125 IU/d vitamin D. Isoflavone amounts Placebo: 0 mg/day Mid-dose: 40mg/day High-dose: 80 mg/day **Duration:** 1 year	Rate of change in BMC was significantly higher in high-dose group compared to placebo and mid-dose groups. Effect was mild and only found in women with initial BMC < median.
Chen YM, 2004 [60]	RCT with 3 groups: placebo, mid-dose, and high-dose, in pill form	• Postmenopausal women • Chinese • Ages 48–62 • N=203	All supplements contained 500mg/d calcium and 125 IU/d vitamin D. Isoflavone amounts Placebo: 0 mg/day Mid-dose: 40mg/day High-dose: 80 mg/day **Duration:** 1 year	Rate of change in BMC was significantly effected by isoflavones in later postmenopausal women (years since menopause>4), lower body weight (<55.5 kg), and lower calcium intake.
Uesugi, 2002 [40]	RCT with 2 groups: soy isoflavone capsule and placebo	• Perimenopausal women • Ages 40–62 • N=23	Soy isoflavone capsule contained 61.8 mg of isoflavones. **Duration:** 4 weeks	Excretion of bone resorption markers was reduced significantly in the isoflavone group. BMC or BMD not tested.

Author, year	*Design*	*Subjects*	*Intervention type, dose, and duration*	*Outcome*
Kreijkamp-Kaspers, 2004 [34]	RCT with 2 groups: ISP or casein protein	• Postmenopausal women • Ages 60–75 • n=202	ISP contained 25.6 g/day of soy protein and 99mg/day of isoflavones. **Duration:** 12 months	Bone mineral density did not differ between the groups after 1 year.
Gallagher, 2004 [36]	RCT with 3 groups: ISP with high, low, or no isoflavone	• Postmenopausal women • Mean age=55 • N=65	High isoflavone 96mg/d Low isoflavone 52 mg/d No isoflavone <4mg/d **Duration:** 9 months	No effect of any of the ISP supplements on BMD in spine or femoral neck.
Dalais, 1998 [61]	RCT with crossover design and 2 arms: wheat/soy arm and wheat/linseed arm	• Postmenopausal women • Ages 45–65 • N=52	Wheat, linseed, and soy were baked into bread which was substituted for usual bread intake. **Duration:** 12 weeks each diet	No changes in BMD found between the groups. BMC increased by 5.2% after the soy phase (significant). No increases in BMC after wheat or linseed phase.
Roughead, 2005 [37]	Controlled feeding study with crossover design. 2 groups: control diet and soy diet	• Postmenopausal women • Ages 52–69 • N=13	In soy diet, 25g high-isoflavone soy protein was substituted for an equivalent amount of meat protein. **Duration:** 7 weeks each diet	Diet did not affect biomarkers of bone retention.
Dalais, 2003 [20]	RCT with 2 groups: ISP or casein placebo supplement	• Postmenopausal women • Ages 50–75 • n=106	ISP contained 40 g/day of soy protein and 118 mg isoflavones. **Duration:** 3 months	No significant differences in markers of bone resorption between placebo and control groups.
Arjmandi, 2005 [62]	RCT with 2 dietary treatments: soy or control	• Postmenopausal women • Age <65 years old • n=87	Soy diet contained 25g soy protein/day and 60mg isoflavones. Control diet contained no soy or isoflavones. Foods were provided to participants **Duration:** 1 year	Both soy and control groups significantly decreased whole body and lumbar BMC and BMD. Both soy and placebo treatments positively affected markers of bone formation.

* Abbreviations: RCT=Randomized Controlled Trial, NCEP=National Cholesterol Education Program, ISP=Isolated Soy Protein, HT=hormone therapy

Table 4

Randomized, Controlled Trials of Red Clover for bone in postmenopausal women

Author, year	*Design*	*Subjects*	*Intervention type and duration*	*Outcome*
Clifton-Bligh, 2001 [42]	RCT with 3 groups. One month of placebo period followed by 6 months of treatment and 1 month of placebo washout. Placebo periods were single blinded.	• Postmenopausal women • Mean age range 55–59 • n=46	The three doses of Rimostil were: 28 mg/d, 57 mg/d, and 85.5 mg/d of isoflavones. **Duration**: 6 months	BMD of radius and ulna increased significantly for women in medium and high treatment groups. **Safety:** endometrial thickness did not change significantly during treatment.
Atkinson, 2004 [45]	RCT with 2 groups: Placebo or isoflavone tablet	• Pre, peri, and postmenopausal women • Ages 49–65 • N=205	Promensil tablet was uses as treatment. One tablet per day in intervention group. **Duration:** 12 months	Loss of lumbar spine BMC and BMD significantly lower in women taking supplement. Bone formation markers significantly increased in supplement group.
Schult, 2004 [43]	RCT with 3 groups: Promensil®, Rimostil®, and placebo	• Perimenopausal women • Ages 45 to 60 • n=250	Promensil: Red clover extract with 41 mg isoflavones per tablet Rimostil: Red clover extract with 28.6 mg isoflavones per tablet. Two tablets per day of each treatment. **Duration:** 12 weeks	No significant differences between groups in bone turnover markers

* Abbreviations: RCT=Randomized Controlled Trial, BMD=bone mineral density, BMC=bone mineral content

Table 5

Randomized, Controlled Trials of Soy or red clover for cognition in postmenopausal women

Author, year	*Design*	*Subjects*	*Intervention type and duration*	*Outcome*
Duffy, 2003 [69]	RCT with 2 groups: soy isoflavone supplement or placebo	• Postmenopausal women not on other forms of hormone therapy • Ages 50–65 • n=33	Supplement contained total of 60mg isoflavones. **Duration:** 12 weeks	Significant improvements in recall of pictures and sustained attention tasks compared to placebo. Significantly greater improvements in learning rule reversals and a planning task
File, 2005 [70]	RCT with 2 groups: soy isoflavone supplement or placebo	• Postmenopausal women not on other forms of hormone therapy • Ages 51–66 • n=50	Supplement contained total of 60mg isoflavones. **Duration:** 6 weeks	Significant improvements in short-term memory, frontal lobe function, mental flexibility, and planning ability in soy group compared to placebo.
Kritz-Sliverstein, 2003 [71]	RCT with 2 groups: isoflavone supplement or placebo	• >2 years postmenopausal • not using estrogen therapy • Ages 55–74 • n=56	Supplement contained a total of 110 mg/day of isoflavones **Duration:** 6 months	Significant improvement in cognitive function, for women on supplement compared to placebo.
Kreijkamp-Kaspers, 2004 [34]	RCT with 2 groups: ISP or casein protein	• Postmenopausal women • Ages 60–75 • n=202	ISP contained 25.6 g/ day of soy protein and 99mg/day of isoflavones. **Duration:** 12 months	No differences in cognitive function between the two groups
Howes, 2005 [46]	RCT with 2 groups: Red clover isoflavones or placebo	• Postmenopausal women • Age >60 • n=30	Supplement contained total of 28.5mg of isoflavones, took 2 tablets a day. **Duration:** 6 months	No effects (after correction for multiple comparisons) of isoflavones on cognitive function.

* Abbreviations: RCT=Randomized Controlled Trial, ISP=Isolated Soy Protein