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Review

Dietary phytoestrogens and health

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Abstract

The interest in the potential health effects of dietary phytoestrogens has increased with the findings that hormone replacement therapy is not as safe or effective as previously thought. This review summarizes the dietary sources of the phytoestrogens; isoflavonoids, stilbenes, coumestans and lignans. It also examines 105 clinical studies related to effects of phytoestrogens on bone density, cardiovascular health, cancer prevention, cognitive ability and menopausal symptoms.

Keywords: Phytoestrogen; Estradiol; Isoflavonoids; Lignans; Stilbenes; Coumestans; Health effects; Phytochemicals; Natural products

Contents

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1. Introduction

The interest in plant derived estrogens—or phytoestrogens—has recently been increased by the realization that hormone replacement therapy is not as safe or effective as previously thought (Hays et al., 2003). The prevalence of phytoestrogens in our diets and the biological effects that they may cause need to be fully examined. This review summarizes what is known about the distribution of phytoestrogens in the diet as well as some of the physiological activities of these compounds. Although this topic has been recently reviewed (Fitzpatrick, 2003; Rowland et al., 2003; Setchell and Lydeking-Olsen, 2003) this review examines 105 clinical studies related to the effects of phytoestrogens on bone density, cardiovascular health, cancer prevention, cognitive ability and menopausal symptoms.

Estrogens, produced in the ovaries and testis, have many biological effects in the body beyond the reproductive system. The estrogen receptors localized in the nucleus and form dimers when bound to an estrogen. The dimers then interact with the estrogen response element (ERE), which regulates transcription of estrogen responsive genes. A small percentage (2–3%) of estrogen receptors are located on the cell membrane and contribute to non genomic effects of estrogen (Norfleet et al., 1999; Razandi et al., 1999; Xu et al., 2003; Chen et al., 2004). There are two known estrogen receptors, ERα and ERβ. Although the two estrogen receptors can be localized within the same cell, they vary in tissue distributions and can have different effects on mixed agonists and antagonists (Nilsson and Gustafsson, 2002). Both ERα and ERβ function in normal ovarian follicular development, vascular endothelia cells, myocardial cells, smooth muscle, and breast tissue (Nilsson and Gustafsson, 2002). ERα is involved in bone maturation in both males and females, however, only ERβ plays a role in bone maintenance in females (Nilsson and Gustafsson, 2002). ERα is more important in maintaining follicle stimulating and luteinizing hormone concentrations in blood, and ERβ is involved in frontal lobe mediated learning and memory (Nilsson and Gustafsson, 2002). The dominant form of estrogen in the body is 17β estradiol (Fig. 1), although any compound that induces receptor dimerization and subsequent binding to the ERE, can be considered an estrogen. Antagonistic effects can occur when a compound is able to bind to the receptor but dimer formation either does

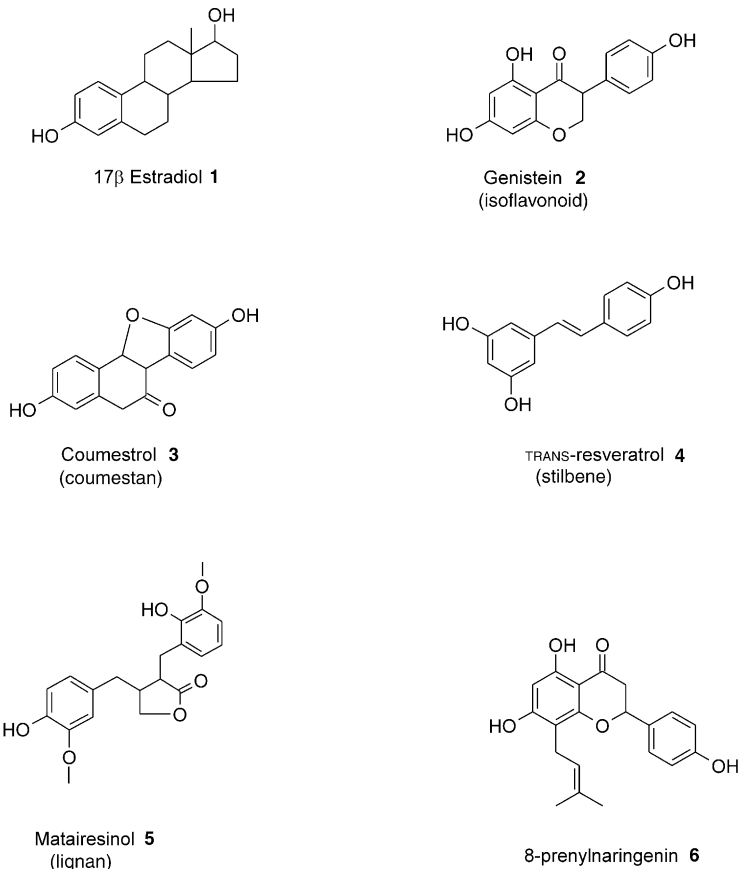

Fig. 1. Structure of 17β-estradiol **1**, genistein **2** (isoflavonoid), coumestrol **3** (coumestan), *trans*-resveratrol **4** (stilbene), matairesinol **5** (lignan) and 8-prenyl naringenin **6**.

not occur or the correct configuration to activate the ERE is not attained. Some compounds act as estrogen agonists and antagonists and are referred to as Selective Estrogen Receptor Modulators (SERMs). As an example, the antiestrogen tamoxifen acts as an estrogen antagonist in breast tissue but as an agonist in the uterus, bone and vascular system (Macgregor and Jordan, 1998). These agonist/antagonistic effects are believed to be responsible for the differential effects of phytoestrogens compared to estradiol. There are several recent reviews on estrogen receptors and SERMs (Nilsson and Gustafsson, 2002; Gustafsson, 2003; Meegan and Lloyd, 2003; Riggs and Hartmann, 2003).

2. Phytoestrogens

In the 1940s it was first realized that some plant-derived compounds could cause an estrogenic effect (Bennetts et al., 1946). Sheep that were grazing on pastures containing red clover had multiple fertility problems. Immature animals were showing signs of estrus, ewes were unable to get pregnant and those that were pregnant often miscarried. The clover in these pastures had high amounts of the isoflavones, formononetin and biochanin A (Rossiter and Beck, 1966), which were among the first phytoestrogens discovered.

Currently, four different families of phenolic compounds produced by plants are considered phytoestrogens: the isoflavonoids, stilbenes, lignans and coumestans (Fig. 1). Different classes of phytoestrogens and diverse compounds within each class affect the estrogen-mediated response in different ways. Below we summarize the effects of each class of phytoestrogens.

3. Isoflavonoids

The flavonoids are a large chemical class that are formed through the phenylpropanoid-acetate biodemial pathway via chalcone synthase and condensation reactions with malonyl CoA. The isoflavonoids are a subclass of flavonoids, where one phenolic ring has migrated from C-3 to C-2. The isoflavonoids from legumes, including genistein **2** and daidzein, are the most studied phytoestrogens. They can exist as glucosides or as aglycones, the glucosides being readily hydrolyzed in the gut to their aglycones. The aglycones are easily transported across intestinal epithelial cells (Dixon and Ferreira, 2002). Genistein **2** has one-third the potency of estradiol **1** when it interacts with ERβ, and one thousandth of the potency of estradiol **1** when it interacts with ERα as determined by expression of luciferase reporter gene construct in kidney cells that had been cotransfected with ERα and ERβ (Kuiper et al., 1998). Genistein **2** can induce similar responses in breast, ovarian, endometrial, prostate, vascular, and bone tissues and cell lines as estradiol **1** (Liu et al., 2001; Davis et al., 2002; Wang et al., 2003; Zhou et al., 2003).

Genistein **2** can act as an estrogen antagonist in some tissues. Exposure of neonatal prepubertal Sprague–Dawley rats to estradiol **1** increased the number of terminal end buds and cell proliferation in mammary tissue (Whitten and Patisaul, 2001); however, exposure to genistein **2** reduced the number of terminal end buds and cell proliferation (Murrill et al., 1996). In mice and rat models, genistein **2** inhibited the development and growth of chemically induced tumors in the breast (Fritz et al., 1998), and prostate (Mentor-Marcel et al., 2001; Fritz et al., 2002). Genistein **2** and other isoflavonoids may exert this effect through induction of a signal transduction pathway leading to apoptosis (Yanagihara et al., 1993).

Genistein **2** has demonstrated effects that are not normally associated with the ER including the ability to inhibit tyrosine kinase and DNA topoisomerase . The inhibition of these enzymes is unchanged even in the presence of an antiestrogen (Jonas et al., 1995). Non-genomic effects could play a role in the differences between genistein **2** and estradiol **1**. Not all isoflavonoids, however, demonstrated these non-genomic effects. The closely related isoflavonoid, daidzein, had no effect on tyrosine kinase or DNA topoisomerase. Other non-ER related effects might be related to the phytoestrogen specific gene recently discovered in MCF-7 cells. This gene is upregulated by genistein **2** and unresponsive to estradiol **1** (Ramanathan and Gray, 2003). The biological significance of this gene is unknown.

Genistein **2** has differential effects on cell cycle progression in neoplastic (MCF-7) and non-neoplastic (MCF-10F) human breast cells (Singletary et al., 2002). It increased cyclin B1 expression and phosphorylation of $p34^{cdc2}$ in the non-neoplastic cell line and had no effect on the neoplastic cell line (Singletary et al., 2002). Genistein **2** inhibited cell proliferation and blocked the cell cycle at G2 in the non-neoplastic cell line at 15 μM, a physiological concentration. The neoplastic cell line was not as sensitive to the presence of genistein **2**, with blockage of the cell cycle occurring only at concentrations of 60 μM and higher (Singletary et al., 2002). The ability of genistein **2** to block cell proliferation of normal mammary cells may contribute to the preventive effect of a high soy diet on risk of breast cancer.

The major source of isoflavonoids in the diet is from soy-based foods (Table 1). In Asia, the intake of soy can be as high as 30–50 g a day and plasma concentrations of genistein **2** from 0.1–10 μM have been measured (Adlercreutz et al., 1993). Although fermentation of soy can reduce the amount of isoflavonoids present by a factor of 2–3 (Wang and Murphy, 1994a,b), bioavailability of isoflavonoids is higher in fermented

products, so urinary excretion rates are similar for people consuming fermented and unfermented products (Hutchins et al., 1995; Slavin et al., 1998). Even though genistein **2** has relatively low potency compared to estradiol **1**, high concentrations in plasma may be sufficient to cause a variety of physiological effects.

A closely related compound to the isoflavonoids is 8-prenyl naringenin **6**, a flavanone, found in beer ingredient hops (*Hummulus lupulus*) (Fig. 1). Before identification of this component, the estrogenic potential of hops was widely debated. The in vivo potency of this compound is weak, with 100 μg/ml of 8-prenyl naringenin **6** administered in drinking water (equivalent to 15 mg/kg/day) being the lowest dose to cause estrogenic effects in ovarectomized mice (Milligan et al., 2002). This is 500 times greater than the concentration of 8-prenyl naringenin **6** in beer.

4. Stilbenes

Stilbenes, like the flavonoids, are produced through the phenylpropanoid-acetate pathway. The main dietary source of phytoestrogenic stilbenes is resveratrol **4** from red wine and peanuts. Although there are two isomers of resveratrol **4**, *cis* and *trans*, only the *trans* form has been reported to be estrogenic (Gehm et al., 1997). Resveratrol **4** is not found in the grape flesh, only in the skin, resulting in low levels of *trans*-resveratrol **4** in white wine (Table 2). The content of resveratrol **4** in wine

Table 1
Isoflavonoid content of selected legumes and soy-based foods

Food	Genistein **2** (mg/100g)	Daidzein (mg/100g)	Total isoflavonoids (mg/100g)[a]	Reference
Soy based infant formula	1.6–15	0.8–9.7	2.6–31	Murphy et al., 1997; USDA, 2002
Soy milk	1.1–11.3	1.1–9.8	1.3–21	Coward et al., 1993; USDA, 2002
Soybeans, mature	1.1–150	0.5–91	1.7–221	Wang et al., 1990; Mazur et al., 1998; USDA, 2002
Tofu	5.0–42.1	0.6–25.6	3.6–67.5	Wang et al., 1990; Coward et al., 1993; USDA, 2002
Phaseolus vulgaris (kidney, navy and pinto bean)	0.007–0.5	0.008–0.04	0.015–0.5	Mazur et al., 1998
Chick peas	0.07–0.2	0.01–0.2	1.1–3.6	Mazur et al., 1998; USDA, 2002

[a] Totals include other flavonoids—formomonetin and biochanin A.

Table 2
Trans-resveratrol **4** level in wine and other plant products

	Trans-resveratrol **4** content (μg/ml)	Reference
Wine		
Muscadine	4.9–13.4	Lamikanra et al., 1996
Beaujolais	3.3–3.6	McMurtrey et al., 1994
Cabernet sauvignon	0.38–8.9	Lamuela-Raventós et al., 1995, McMurtrey et al., 1994, Klinge et al., 2003, Lamikanra et al., 1996, Creasy and Creasy, 1998, Chu et al., 1998, Frankel et al., 1995
Cabernet franc	2.0	Creasy and Creasy, 1998
Petite Sirah	0.3–2.2	Frankel et al., 1995
Pinot noir	1.0–8.0	Lamuela-Raventós et al., 1995, McMurtrey et al., 1994, Creasy and Creasy, 1998, Chu et al., 1998, Frankel et al., 1995
Burgundy	1.1–1.3	Lamikanra et al., 1996
Merlot	1.0–15.3	Lamuela-Raventós et al., 1995, Lamikanra et al., 1996, Creasy and Creasy, 1998, Chu et al., 1998, Frankel et al., 1995
Zinfandel	0.6–3.6	McMurtrey et al., 1994, Lamikanra et al., 1996, Frankel et al., 1995
Concord	1.1–2.7	Lamikanra et al., 1996
White wines	0–0.3	Creasy and Creasy, 1998, Frankel et al., 1995, Klinge et al., 2003
Plant products	*Trans*-resveratrol **4** content (mg/100g)	
Peanut butter	0.015–0.98	Ibern-Gomez et al., 2000, Sobolev and Cole, 1999
Peanuts	0.003–0.07	Sanders et al., 2000, Sobolev and Cole, 1999
Green peanuts	0.18–0.71	Sobolev and Cole, 1999
Polygonum cuspidatum	296–377	Vastano et al., 2000
California table grapes	0.016–0.3	Creasy and Creasy, 1998
Raisins	0.0005–0.003	Creasy and Creasy, 1998
Grape juice–purple	0.08	Creasy and Creasy, 1998
Grape juice- white	0.001	Creasy and Creasy, 1998

depends on cultivar, geographic location, season, oenological practices and presence of Botrital fungus (Frankel et al., 1995; Creasy and Creasy, 1998; Fremont, 2000). The longer the fermentation time the more *trans*-resveratrol **4** will be in the final product. The level of *trans*-resveratrol **4** in red wines, fermented with skins, can be as high 14.5 mg/l (Lamikanra et al., 1996; Fremont, 2000).

The type of post harvest processing has a large effect on the resveratrol **4** content in the final product. This is evidenced by purple grape juice containing more resveratrol **4** than white grape juice (Table 2). White grape juice is made by cold pressing the grapes, while a hot extraction method is used for purple grape juice (Creasy and Creasy, 1998). This is also true for peanuts, with boiled peanuts containing more resveratrol **4** than peanut butter and roasted peanuts (Sobolev and Cole, 1999). As the peanut matures, the resveratrol **4** content in the nut declines, with smaller peanuts having higher levels of resveratrol **4** (Sobolev and Cole, 1999). In peanuts, resveratrol **4** is found throughout the nut: however on a weight basis the seed-coat has the highest levels (Sanders et al., 2000).

The roots of *Polygonum cuspidatum* (Japanese Knotweed or Mexican Bamboo) are used in traditional Chinese medicine for a variety of therapeutic purposes. The resveratrol **4** levels in the dried root can be as high as 377 mg /100 g dry root (Vastano et al., 2000). In addition to these food products, resveratrol **4** has been isolated from several grass species (Powell et al., 1994) pine bark (Mannila and Talvitie, 1992) ivy and lilies (Creasy and Creasy, 1998).

Resveratrol **4** has high bioavailability and physiological levels can be obtained through drinking red wine (Schmitt et al., 2002). It has a greater capacity to activate the ERβ than ERα (Klinge et al., 2003). Resveratrol **4** has shown agonistic and antagonistic activity in MCF-7 cells and the hamster ovarian cell line, CHO-K1, transfected with human ERα and ERβ (Lu and Serrero, 1999; Bowers et al., 2000; Brownson et al., 2002)

5. Lignans

The term lignan is used for a diverse class of phenylpropanoid dimers and oligomers. Secoisolariciresinol and matairesinol **5** are two lignan dimers that are not estrogenic by themselves, but are readily converted to the mammalian lignans, enterodiol and enterolactone, respectively, which are estrogenic (Setchell et al., 1981; Glitsø et al., 2000). The conversion occurs by gut microflora and the mammalian lignans are readily absorbed. The phytolignans appear in high amounts in flaxseed, whole grain breads, vegetables, and tea. Fruits have low levels of these lignans with the exception of strawberries and cranberries (Table 3).

6. Coumestans

Although there are a large number of coumestans, only a small number have shown estrogenic activity, predominantly coumestrol **3** and 4′ methoxycoumestrol. The main dietary source of coumestrol, is legumes; however low levels have been reported in brussel sprouts and spinach (Knuckles et al., 1976; Wang et al., 1990; Franke et al., 1994). Clover and soybean sprouts are reported to have the highest concentration, 28 and 7 mg/100 g dry wt., respectively; mature soybeans only have 0.12 mg/100 g dry wt (Knuckles et al., 1976; Wang et al., 1990; Franke et al., 1994).

7. Health effects

There have been many clinical and epidemiological studies examining the health effects of phytoestrogen-

Table 3
Secoisolariciresinol and matairesinol **5** content of selected foods

Food	Secoisolariciresinol (mg/100 g dry wt.)	Matairesinol **5** (mg/100g dry wt.)	Total lignan content (mg /100 g dry wt.)	Reference
Flaxseed	9–370	1	9–370	Childress et al., 1997
Whole grain breads	N.A.[a]	N.A.	<0.1–14.5	Nesbitt and Thompson, 1997
Black gram	0.046–0.240	0.08–0.262		Mazur et al., 1998
Kidney bean	0.056–0.153	Trace		Mazur et al., 1998
Soybean	0.013–0.273	Trace		Mazur et al., 1998
Squash	N.A.	N.A.	6.3	Thompson et al., 1991
Iceberg lettuce	N.A.	N.A.	2.6	Thompson et al., 1991
Tomato	0.05	0.006	0.06–0.3	Thompson et al., 1991; Mazur, 1998
Tea	N.A.	N.A.	2.7	Mazur et al., 1999
Apples	N.A	N.A	0.2	Thompson et al., 1991
Cranberries	1.5	0		Meagher and Beecher, 2000
Strawberries	1.5	0.08	1.6	Mazur, 1998

[a] Data not available, only totals reported.

containing supplements and foods (Table 4). The full summary of the clinical and epidemiological studies used in this review (Table 5). Most studies have examined the effects in peri/postmenopausal women (70), but some studies included pre-menopausal women (33), men (16), and infants (1). Below we summarize the clinical studies of phytoestrogens according to the clinical endpoints.

8. Bone density

Estrogen plays an important role in maintaining bone density by regulating the formation and resorption of bone (Nilsson and Gustafsson, 2002). Since lower circulating estradiol **1** levels are found during menopause, calcium is lost from the bone into blood plasma, leading to osteoporosis (Yamaguchi, 2002). One of the aims of hormone replacement therapy (HRT) is to prevent or lower the incidence of osteoporosis in postmenopausal women. Most of the studies suggest that phytoestrogens are somewhat effective in maintaining bone mineral density (BMD) in postmenopausal women (Table 4) (Dalais et al., 1998; Kardinaal et al., 1998; Alekel et al., 2000; Ho et al., 2001; Mei et al., 2001; Chiechi et al., 2002; Kim et al., 2002; Morabito et al., 2002). A double blind placebo controlled study of postmenopausal women showed significant increase in BMD at the femoral neck after 12 months of daily administration of 54 mg genistein **2**, isolated from soy, although a significant increase in osteocalcin and bone specific alkaline phosphatase (BAP) was also observed (Morabito et al., 2002). In contrast 17β-estradiol **1** increased BMD with a significant decrease in osteocalcin and BAP levels (Morabito et al., 2002). In a 24-week study comparing isoflavone rich soy protein (80.4 mg aglycone isoflavones/ day) and isoflavone poor soy protein (4.4 mg aglycone isoflavones/ day) in perimenopausal women, both BMD and bone mineral content (BMC) were significantly higher with the diet high in isoflavones (Alekel et al., 2000). There was no significant change in the BMD or BMC of the lumbar spine over the 24 weeks for the women on either the high or low isoflavone soy protein diet; however, the woman on the control diet had a significant decrease of BMD and BMC during this time. The women who had more bone loss had higher BAP levels. Therefore BAP may be a better indicator of bone turnover than bone formation (Alekel et al., 2000).

The lumbar spine seems to benefit the most from consumption of soy phytoestrogens. A 24-week long study with postmenopausal women consuming soy protein with 90 mg isoflavones/day showed a significant increase in BMD of the lumbar spine, with no effect on the femoral neck or total body BMD (Potter et al., 1998). There were no BMD effects in woman consuming soy protein with 56 mg isoflavones/day (Potter et al., 1998). The only study to examine the effects of soy isoflavones in premenopausal women showed no effect on bone mineral density levels (Mei et al., 2001), while significant effects were observed in postmenopausal women in this study.

Table 4
Summary of phytoestrogen clinical studies

	Positive results	Total
Clinical endpoints		
Maintaining bone density	11	15
Relief menopause symptoms	4	17
Cardiovascular benefit	25	38
Cancer prevention	7	13
Hormone levels/menstrual cycle	12	19
Effect on hormones in men	0	1
Immune system	1	1
Neurological	5	5
Total[a]	64	105
Type of phytoestrogens		
Soy isoflavonoids	41	70
Clover isoflavonoids	2	5
Lignans	15	23
Other [b]	3	4
Genistein **2**	3	5
Ipriflavone	1	1
Subjects		
Peri/post menopausal women	42	70
Pre menopausal women	21	33
Men	7	16
Infants	1	1

[a] Totals are less than the sum of the studies since some studies examined several clinical endpoints.

[b] Includes mixtures of *Cimcifuga racemosa* (Black cohosh), *Angelica sinensis* (Dong quai), soy and *Pueriara lobata*.

9. Cardiovascular health

In postmenopausal women, cardiovascular disease (CVD) is the leading cause of death in the US (CDC, 2002). Estrogen can affect the vascular system both directly, through the ERs located in vascular tissue, and indirectly through altering the lipoprotein profile (Rubanyi et al., 2002). Initial epidemiological studies showed that women taking HRT were 50% less likely to experience severe CVD. These women were followed for an average of 3 years (Stampfer et al., 1985; Lissin and Cooke, 2000; Rubanyi et al., 2002). However, a more comprehensive study performed by The Women's Health Initiative has demonstrated that there is a significant increase in CVD in the first year of use and the risk is still elevated after 5 years of continued use (Hays et al., 2003; Manson et al., 2003). In fact, this study was halted early because the risk of CVD and stroke was strongly elevated (Writing Group for the Women's

Table 5
Summary of clinical and epidemiological studies of phytoestrogens

Phytoestrogen	Subjects	Amount of phytoestrogen	Study design	Number patients/ country	Endpoint	Length of study (time on PE)	Result	Reference
Cimcifuga racemosa	Post menopause	40 mg/day	Double blind, placebo	62/Germany	Bone, menopause symptoms	12 weeks	Reduction in symptoms, increase bone biomarkers	Wuttke et al., 2003
Flaxseed	Hypercholestemic post menopause	40 g/day	Crossover, conjugated equine estrogens, diet alone	25/Canada	LDL, HDL cholesterol, menopausal symptoms, glucose insulin levels	2 months	Decrease LDL, menopause symptoms, glucose, insulin, increase in HDL apolipoprotein a	Lemay et al., 2002
Flaxseed	Post menopause	40 g/day	Double blind, control	36/USA	Total cholesterol, LDL, HDL, apolipoprotein, bone markers	3 months	Decrease total, LDL cholesterol, no effect HDL, apolipoprotein, bone markers	Lucas et al., 2002
Genistein **2**	Post menopause	54 mg/day	Double blind placebo, HRT	90/Italy	Bone ALP, osteocalcin, BMD	1 year	Significant increase	Morabito et al., 2002
Genistein **2**	Post menopause	54 mg/day	Double blind, control	60/Italy	Plasma endothelin level, nitric oxide breakdown products	6 months	Increase/ decrease respe.	Squadrito et al., 2002
Genistein **2**	Post menopause	54 mg/day	Double blind, control	79/Italy	Endothelial function	1 year	Increase endothelial function	Squadrito et al., 2003
Genistein **2**	Men, with prostate cancer	450–900 mg/day	Case control	20/USA	Genotoxicity in peripheral lymphocytes	84 days	No effect	Miltyk et al., 2003
Genistein **2** and enterolactone	Post menopause women	Diet	Tertiles of intake	400/the Netherlands	Development of breast cancer, urinary excretion	Urine samples collected 1–9 years before	No significant difference in groups and risk of breast cancer	den Tonkelaar et al., 2001
Enterolactone	Men	Dietary	Quartiles of intake	1889/Finland	CVD		Decrease risk correlated with higher serum enterolactone concentrations	Vanharanta et al., 2003
Enterolactone	Men	Dietary	Case control	428/Finland	Prostate cancer		No correlation between serum levels and risk of prostate cancer	Kilkkinen et al., 2003
Ipriflavone (synthetic isoflavonoid)	Post menopause	400–600 mg/day	Calcium supplement	52/Italy	Bone density, plasma osteocalcin	2 years	No change osteocalcin, increase in bone density	Gambacciani et al., 1997
Isoflavonoids	Men	40 mg/day	Self control	12/UK	Semen quality, testicular volume, hormone levels	2 months	No effect	Mitchell et al., 2001
Isoflavonoids	Post menopause hyper cholesterolemic	56, 90 mg/day	Double blind	66/USA	Blood lipid metabolism, BMD	6 months	Decrease total, LDL cholesterol, increase HDL and BMD	Potter et al., 1998
Isoflavonoids	Post menopause with high testosterone	1 soy dish daily	Controls encouraged to eat fruit and veggies	99/Italy	Testosterone, estradiol **1** and SHBG levels	4.5 months	SHBG increased, testosterone decreased, no sig difference in estradiol **1**	Berrino et al., 2001
Isoflavonoids	Post menopause/ breast cancer survivors	114 mg/day	Double blind, crossover	56/Finland	Menopause symptoms	3 months	No different than placebo	Nikander and et al., 2003
Isoflavonoids	Post/pre menopause	Dietary	Case control	620/Singapore	Breast cancer		High soy decrease risk in pre menopause not for post	Lee et al., 2003

(*continued on next page*)

Table 5 (*continued*)

Phytoestrogen	Subjects	Amount of phytoestrogen	Study design	Number patients/ country	Endpoint	Length of study (time on PE)	Result	Reference
Isoflavonoids and lignans	Post menopause	Dietary	Quartiles	403/ The Netherlands	Aortic stiffness		Trend for decrease with higher intakes	Van der Schouw et al., 2002
Isoflavonoids and lignans	Post menopause	Dietary	Quartiles of intake	939/US	Waist to hip ratio, blood pressure, lipoprotein levels		WHR lower, lowest plasma triglycerides in women highest intake,	De Kleijn et al., 2002
Isoflavonoids, lignans	Post menopause	Dietary	Intake levels	30/Finland	SHBG, estrogens		Increase urinary enterolactone excretion correlated increase plasma SHBG,	Adlercreutz et al., 1992
Isoflavonoids, clover	Men and women (post and pre meno) with high blood pressure	55 mg/day	Double blind	59/Australia	Blood pressure	8 weeks	No effect	Hodgson et al., 1999
Isoflavonoids, clover	Post menopause	28.5, 57, or 85.5 mg/day	Double blind, control	46/Australia	HDL, serum apolipoprotein, endometrial thickness, bone mineral density	6 months	HDL and BMD increased, apolipoprotein decreased, no change endometrial thickness	Clifton-Bligh et al., 2001
Isoflavonoids, clover	Post menopause	0, 57, 82 mg/day	Double blind, placebo	246/USA	Hotflashes	12 weeks	No difference than placebos, reduction from baseline	Tice et al., 2003
Isoflavonoids, clover	Post menopause, hypercholesterolaemia	43.5, 87 mg/day	Double blind cross over	75/Australia	Cholesterol levels	12 weeks	No effect	Howes et al., 2000
Isoflavonoids, clover, soy	Post menopause	55 mg/day		25/Spain	Prostacyclin production in vitro	6 months	Increased compared to baseline	Garcia-Martinez et al., 2003
Isoflavonoids, lignans	Post menopause	Dietary		75/Korea	Urinary excretion and BMD		Correlation with enterolactone	Kim et al., 2002
Isoflavonoids, lignans	Post menopause	Dietary		67/the Netherlands	Urinary excretion and correlation with bone loss	5 years	No association	Kardinaal et al., 1998
Isoflavonoids, lignans	Post/pre menopause	Dietary	Case control	3015/China	Urinary excretion of phytoestrogens		Reduced risk with increasing excretion	Dai et al., 2002
Isoflavonoids, lignans	Post/pre menopause	Dietary	Case control	288/Australia	Urinary excretion of phytoestrogens		Reduced risk with increasing excretion	Ingram and Sanders, 1997
Isoflavonoids, lignans	Pre and post menopause	Dietary	Quintiles	111 526/USA	Breast cancer		No effect	Horn-Ross et al., 2002b
Isoflavonoids, lignans	Women	Dietary	Quintiles	1166/USA	Thyroid cancer		Reduced risk	Horn-Ross et al., 2002a
Isoflavonoids, *Pueraria lobata*	Post menopause	100 mg/day	Placebo	127/Hong Kong	Levels of cholesterol, FSH, cognitive ability	3 months	No change in cholesterol, FSH, improvement cognitive ability	Woo et al., 2003
Isoflavonoids, soy	Breast cancer patients	Dietary	Case Control	120/Shanghai	Urinary excretion of isoflavonoids		Increase risk of breast cancer with lower excretion rates	Zheng et al., 1999
Isoflavonoids, soy	Breast cancer survivors	150 mg/day	Double blind, crossover	175/USA	Hot flashes	4 weeks	No different than placebo	Quella et al., 2000
Isoflavonoids, soy	Male	60 g soy protein	Randomized control	20/Canada	Total cholesterol, HDL, platelet aggregation ex vivo	28 days	No effect	Gooderham et al., 1996

Table 5 (*continued*)

Phytoestrogen	Subjects	Amount of phytoestrogen	Study design	Number patients/ country	Endpoint	Length of study (time on PE)	Result	Reference
Isoflavonoids, soy	Male and female	86 mg/day	Crossover	Canada	Oxidized LDL levels, sex hormone activity (measured ex vivo)	1 month	Decreased LDL oxidation, no effect on sex hormone activity	Jenkins et al., 2000
Isoflavonoids, soy	Male infants	Soy based formula	Partially randomized, control	39/USA	Cholesterol fractional synthesis rates	4 months	Decrease	Cruz et al., 1994
Isoflavonoids, soy	Men and post menopause, healthy	55 mg/day	Double blind, placebo	56/Australia	Serum total, LDL, HDL, triglycerides, lipoprotein (a)	8 weeks	No effect	Hodgson et al., 1998
Isoflavonoids, soy	men and women (post and pre meno) with high cholesterol	5, 27, 37, 62 mg/day	Double blind, placebo	155/US	Serum lipids and lipoproteins	9 weeks	Decrease total, LDL cholesterol; triglycerides, HDL unaffected	Crouse III et al., 1999
Isoflavonoids, soy	Men, post menopause women	73 mg/day	Crossover control dairy, 10 mg day isoflavonoids	41/Canada	Interleukin 6	1 month	Increase in women only	Jenkins et al., 2002
Isoflavonoids, soy	Menopause	70 mg/day	Open study, no control	190/Spain	Alleviating menopausal symptoms: hot flashes, sleep disorder, vaginal dryness, depression, bone pain	4 months	Decrease symptoms	Albert et al., 2002
Isoflavonoids, soy	Peri and Post menopauseal	0, 42, 58 mg/day	Double blind, placebo	241/USA	Vasomotor, hotflashes		No difference than placebos, reduction from baseline	Burke et al., 2003
Isoflavonoids, soy	Peri menopause	34 mg/day	Double blind, crossover, placebo	51/ USA	Cholesterol, vasomotor symptoms, menopausal symptoms	6 weeks	Decline in cholesterol, vasomotor, no sig effects frequency of symptoms	Washburn et al., 1999
Isoflavonoids, soy	Peri menopause	80.4 mg/day	Double blind, placebo	69/USA	Bone mineral density, bone mineral content	24 weeks	Sig loss in controls but no change in soy treated group	Alekel et al., 2000
Isoflavonoids, soy	Post menopause	7.1, 65, 132 mg/day	Crossover	18/USA	Altering estrogen metabolism	93 days	Decreased ratio of genotoxic:total estrogens with increase isoflavonoids	Xu et al., 2000
Isoflavonoids, soy	Post menopause	132 mg/day	Double blind, crossover;	32/UK	Insulin, Cholesterol (total, LDL, Total:HDL ratio), glycosylated hemoglobin,HDL cholesterol, triglycerides, weight, BP	12 weeks	Reduced Insulin, Cholesterol glycosylated haemoglobin, no effect HDL, BP, weight triglycerides	Jayagopal et al., 2002
Isoflavonoids, soy	Post menopause	80 mg /day	Cross over	21/Australia	Arterial elasticity, plasma lipids	2×5 week segments	Improved elasticity, no change plasma lipids	Nestel et al., 1997
Isoflavonoids, soy	Post menopause	50 mg/day	Double blind, placebo	39/Italy	Menopause symptoms	6 weeks	Decreased hot flashes, no effect endometrial thickness metabolic or hormonal parameters	Scambia et al., 2000
Isoflavonoids, soy	Post menopause	60 mg /day	Double blind, control	36/UK	Cognititve tests, menopause symptoms, sleepiness, mood	12 weeks	Increase in cognitive function, no effect menopause, mood, sleepiness	Duffy et al., 2003
Isoflavonoids, soy	Post menopause	165 mg/day	Control—normal diet	91/USA	FSH, LH, SHBG vaginal cytology	4 weeks	No change	Baird et al., 1995

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Table 5 (*continued*)

Phytoestrogen	Subjects	Amount of phytoestrogen	Study design	Number patients/ country	Endpoint	Length of study (time on PE)	Result	Reference
Isoflavonoids, soy	Post menopause	72 mg/ day	Double blind placebo	62/Italy	Reduction in hot flashes, endometrial thickness, arterial flow	6 months	No effect	Penotti et al., 2003
Isoflavonoids, soy	Post menopause	80 mg/day	Double blind crossover, placebo	20/Australia	Blood pressure, plasma lipids, flow mediated endothelium dependent dilation	8 weeks	No effect	Simons et al., 2000
Isoflavonoids, soy	Post menopause	100 mg/day	Double blind placebo—wheat cereal	27/USA	Endometrial stimulation	6 months	No effect	Balk et al., 2002
Isoflavonoids, soy	Post menopause	60 g soy powder	Double blind, placebo	72/Italy	Hot flashes, vaginal maturation	3 months	No effect	Albertazzi et al., 1999
Isoflavonoids, soy	Post menopause	188 mg/day	Double blind, placebo	94/Australia	Menopause symptoms—mild severity	3 months	No difference than placebo	Kotsopoulos et al., 2000
Isoflavonoids, soy	Post menopause and men	118 mg/day	Double blind, control	213/Australia	Cardiovascular disease	3 months	Lower BP, lower LDL:HDL ratio, lower triglycerides, increase in Lp(a)	Teede et al., 2001
Isoflavonoids, soy	Post menopause moderate hypercholestemic	150 mg/day	Double blind, control	36/USA	Serum lipids and lipoproteins	2 months	No effect	Dewell et al., 2002
Isoflavonoids, soy	Post menopause with breast cancer survivors	90 mg/day	Double blind, placebo	123/Canada	Hot flashes	12 weeks	No difference than placebos, reduction from baseline	Van Patten et al., 2002
Isoflavonoids, soy	Post menopause, normo, mild hypercholesterolemic	7.1, 65, 132 mg/day	Crossover trial	18/USA	Cholesterol, lipoprotein (a)	93 days	Decrease in LDL cholesterol, ratio of LDL:HDL, no change in HDL	Wangen et al., 2001
Isoflavonoids, soy	Post/pre menopause	Dietary groupings	Tertiles of intake	650/ Hong Kong	Bone mineral density		Significant difference in post menopause between groups not in premenopause	Mei et al., 2001
Isoflavonoids, soy	Post/pre menopause	38 mg/day	Cross over	38/USA	hormone levels, nipple aspirate, breast cytology	6 months	NAV increase in premenopause, no change in post menopause, or in homone levels	Petrakis et al., 1996
Isoflavonoids, soy	Pre and post menopause	60 mg/day	Crossover	12/USA	Luteinizing hormone concentrations	10–14 days	No effect in premenopausal, slight decrease in post menopausal women	Nicholls et al., 2002
Isoflavonoids, soy	Pre and post menopause	8, 65, 130 mg/day	Double blind, crossover	32/USA	Plasma leptin concentrations	3 menstrual cycles + 9 days or 93 days	No effect	Phipps et al., 2001
Isoflavonoids, soy	Pre menopause	0, 23, 25, 45	Control	15/UK	Hormone levels, menstrual cycle length, cholesterol	9 months	Follicular phase increase, reduction in cholesterol with high dose	Cassidy et al., 1995

Table 5 (*continued*)

Phytoestrogen	Subjects	Amount of phytoestrogen	Study design	Number patients/ country	Endpoint	Length of study (time on PE)	Result	Reference
Isoflavonoids, soy	Pre menopause	10, 65, 129 mg /day	Crossover to each dose	12/USA	Excretion of estrogens	3 menstrual cycles + 9 days	Decrease excretion of estrogens, decrease in genotoxic/total estrogen ratio	Xu et al., 1998
Isoflavonoids, soy	Pre menopause	45 mg/day	Self control	51/UK	Nipple aspirate levels apolipoprotein D, pS2, breast epithelial cell proliferation,	14 days	Weak estrogen effect, no effect on proliferation	Hargreaves et al., 1999
Isoflavonoids, soy	Pre menopause	5 mg/day	Self control	9/USA	Circulating levels of ovarian hormones, gonadotropins	1 menstrual cycle	Decrease in estradiol **1** and progesterone	Lu et al., 2001
Isoflavonoids, soy	Pre menopause	10, 65, 129 mg/day	Crossover	13/USA	Cholesterol, total, HDL, LDL	3 menstrual cycles	Significant decrease	Merz-Demlow et al., 2000
Isoflavonoids, soy	Pre menopause	200 mg/day	Self control	6/USA	Hormone levels, menstrual cycle	1 month	Decrease serum estrogen, progesterone levels, increase cycle length	Lu et al., 1996
Isoflavonoids, soy	Pre menopause	109 mg/day	Control- Normal diet	60/Japan	Serum Estrogen levels, menstrual cycle length	3 menstrual cycles	Non sig decrease in estrogen levels, no change in menstrual cycle length	Nagata et al., 1998
Isoflavonoids, soy	Pre menopause	100 mg/day	Double blind, placebo	34/USA	Menstrual cycle length, hormone levels	1 year	No change length of cycle or hormone levels	Maskarinec et al., 2002
Isoflavonoids, soy	Pre menopause	38 mg/day	Self control	36/USA	Menstrual cycle length, sex hormone levels	2 menstrual cycles	No change	Martini et al., 1999
Isoflavonoids, soy	Pre menopause	86 mg/day	Single blind cross over-placebo	14/Australia	Plasma lipid concentrations, LDL oxidation	2 menstrual cycles	No effect	Samman et al., 1999
Isoflavonoids, soy	Pre menopause with benign or malignant breast disease	45 mg/day	Control	48/UK	In vitro Breast epithelium proliferation, level of progesterone receptor expression	14 day	Increase in proliferation, progesterone receptor	McMichael-Phillips et al., 1998
Isoflavonoids, soy	Pre menopause	Dietary groupings	Quartiles of intake	132/Hong Kong	Spinal bone mineral density	3 years	Sig difference between 1st and 4th	Ho et al., 2001
Isoflavonoids, soy	Pre menopause	45 mg/day	Crossover	6/UK	Menstrual cycle length, hormone levels	1 month	Longer luteal phase, cycle; increase in serum estradiol **1**	Cassidy et al., 1994
Isoflavonoids, soy	Pre menopause and men	100 mg/day	Single blind control 0.5 mg/day	27/UK	Memory, cognitive functions	10 weeks	Improvement in scores	File et al., 2001
Isoflavonoids, soy	Post menopause previous breast cancer	114 mg/day	Double blind, placebo	56/Finland	CRP, E-selectin, NO	3 months	No effect	Nikander et al., 2003
Isoflavonoids, soy	Teenage boys	50 mg/day	Double blind, placebo	128/Australia	BAP, bone turnover	6 weeks	No effect	Jones et al., 2003
Isoflavonoids, soy	Post menopause	80 mg/day	Double blind, placebo	203/Hong Kong	BMD, BMC	1 year	Increase BMC	Chen et al., 2003
Isoflavonoids, soy	Post menopause	120 mg/day	Placebo	39/USA	Protection from estradiol **1** induced endometrial changes	6 months	No protection	Murray et al., 2003
Isoflavonoids, soy	Post menopause	107 mg/day	Double blind, crossover	28/USA	Vascular function	6 weeks	Lower post occlusion peak flow, no improvement other endpoints	Steinberg et al., 2003
Isoflavonoids, soy	Post menopause	110 mg/day	Double blind, crossover	53/USA	Cognitive ability	6 months	Increase in category fluency, no change other abilities	Kritz-Silverstein et al., 2003

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Table 5 (*continued*)

Phytoestrogen	Subjects	Amount of phytoestrogen	Study design	Number patients/ country	Endpoint	Length of study (time on PE)	Result	Reference
Isoflavonoids, soy	Post menopause	118 mg/day	Double blind, placebo	78	Lipid profiles, bone markers	3 months	Improvement lipid profiles–no effect on bone markers	Dalais et al., 2003
Isoflavonoids, soy	Men, post menopause	83 mg/day	Double blind, placebo	150/USA	IGF-1	12 months	No effect	Adams et al., 2003
Isoflavonoids, soy	Pre menopause	100 mg/day	Double blind, placebo	30/USA	Mammogram density	12 months	No effect	Maskarinec et al., 2003
Isoflavonoids, soy	Post menopause (using/not using HRT)	88.4 mg/day	Double blind, placebo	42/USA	IGF-1, bone resorption	3 months	Increase IGF-1, decrease bone resorption, greatest change women not on HRT	Arjmandi et al., 2003
Isoflavonoids, soy	Post menopause, hypercholestemic	25 g soy protein/day isoflavonoid amt not reported	Double blind, placebo	24/Israel	Vascular inflammation	6 weeks	No effect	Blum et al., 2003
Isoflavonoids, soy	Young men and women	56 mg/day	Cross over, control soy protein 1.9 mg/day	22/UK	Lipid peroxidation, LDL oxidation	17 days	Reduced	Wiseman et al., 2000
Isoflavonoids, soy	Young, normocholestemic men and women	56 mg/day	Crossover, control-2 mg/day isoflavonoids	22/UK	HDL-cholesterol, apolipoprotein A	17 days	Increase	Sanders et al., 2002
Isoflavonoids, soy; wheat enterolactones	Post menopause	45 g flour	Double blind	58/Australia	Menopause symptoms, hot flashes	12 weeks	Significant decrease from before study, no sig difference between groups	Murkies et al., 1995
Lignans	Post menopause/ pre menopause	Dietary	Quintiles intake	820/USA	Ovarian cancer		Decrease risk with highest intake	McCann et al., 2003
Lignans	Post menopause/ pre menopause	Serum levels	Case control	208/Finland	Breast cancer and dietary lignan		Decrease risk with highest intake	Pietinen et al., 2001
Lignans	Post menopause/ pre menopause	Dietary	Quintiles intake	1550/USA	Dietary intake and risk of breast cancer		Decreased risk highest intake	McCann et al., 2002
Lignans, flax seed	Post menopause	0, 5, 10 g flax seed day	Cross over	28/USA	Excretion of estrogen metabolites	7 weeks	Increase in chemoprotective metabolites, ratio of good:genotoxic estrogens	Haggans et al., 1999
Lignans, flax seed	Post menopause	0, 5, 10 g flax seed day	Cross over	28/USA	Serum hormone levels and binding proteins	7 weeks	Decrease estradiol **1** and estrone sulphate, increase prolactin	Hutchins et al., 2001
Lignans, flax seed	Pre menopause	10 g flax seed/day	Cross over	18/USA	Length of menstrual phase, ovarian hormones	3 cycles	Luteal phase longer, during LP increase in progesterone:estradiol **1** concentration	Phipps et al., 1993
Mixture	Post menopause	Angelica sinesis extract 750 mg, Cimicifuga racemosa 150mg + other herbs and minerals	Single blind,	12/USA	Bone mineral density	2 years	Significant bone loss over 2 years	Cook and Pennington, 2002

Table 5 (*continued*)

Phytoestrogen	Subjects	Amount of phytoestrogen	Study design	Number patients/country	Endpoint	Length of study (time on PE)	Result	Reference
Mixture Soy isoflavonoids, black cohosh, dong quai	Pre menopause	60 mg isoflavonoids, 100 mg dong quai, 50 mg black cohosh	Placebo	38/USA	Migraines	24 weeks	Reduced frequency	Burke et al., 2002
Soy milk	Post menopause	30 g soy milk/day	Baseline, self control	20/Chile	Sex hormone binding globulin (SHBG) serum levels	10 weeks	Increase correlated to PE serum levels	Pino et al., 2000
Soy rich diet	Post menopause	9 soy meals/week	HRT, control	166/Italy	BMD, osteoblast activity	6 months	No decrease in BMD, increase in osteoblast activity	Chiechi et al., 2002
Soy, linseed	Post menopause	45 g day soy or linseed	Double blind, crossover	44/Australia	Hotflashes, bone mineral density/content, vaginal smears	12 weeks	Not significant	Dalais et al., 1998

Abbreviations: ALP—Alkaline phosphatase; BMD—Bone mineral density; BP—Blood pressure; CR-P—C-Reactive Protein; FSH—Follicle Stimulating Hormone; HDL—High density lipoprotein cholesterol; HRT—Hormone Replacement Therapy; IGF-1—Insulin Like Growth Factor-1; LDL—Low density cholesterol; Lp(a)—Lipoprotein A; NAV—Nipple Aspirate Volume; PE—Phytoestrogens; Post menopause—Women who have gone through menopause or are going through it; Pre menopause—Women who have not started menopause; SHBG—Sex hormone binding globulin.

Health Initiative Investigators, 2002; Hays et al., 2003; Manson et al., 2003). Postmenopausal women who have already developed CVD (with at least one arterial lesion) also did not receive any benefit from 3 years of treatment (Hodis et al., 2003).

There are several clinical studies that have examined the effect that dietary phytoestrogens have on CVD. Isoflavonoids or soy/soy protein and flaxseed have the ability to lower total cholesterol (Potter et al., 1998; Crouse III et al., 1999; Washburn et al., 1999; Merz-Demlow et al., 2000; Jayagopal et al., 2002; Lucas et al., 2002), LDL cholesterol (Potter et al., 1998; Merz-Demlow et al., 2000; Teede et al., 2001; Wangen et al., 2001; Jayagopal et al., 2002; Lemay et al., 2002; Lucas et al., 2002) and to raise HDL (Potter et al., 1998; Sanders et al., 2002). It should be noted that the longest of these studies was six months and HRT produced improvement in short-term studies. Soy may affect the synthesis of cholesterol even in newborns, as male infants fed soy-based formula had lower cholesterol fractional synthesis rates than infants fed breast milk or cow milk-based formula (Cruz et al., 1994). However, several studies showed no effect of isoflavonoids derived from soy or red clover on serum cholesterol levels (Gooderham et al., 1996; Hodgson et al., 1998; Howes et al., 2000) or plasma lipids (Samman et al., 1999; Simons et al., 2000; Dewell et al., 2002).

Two studies that examined the dietary intake of lignans and isoflavonoid containing foods in post-menopausal women showed that the quartile with the highest intake had a more favorable waist to hip ratio, triglyceride levels, metabolic score (De Kleijn et al., 2002) and aortic stiffness (Van der Schouw et al., 2002) than women with the lowest intake. No correlation was found between the intake of phytoestrogens and blood pressure, total, LDL and HDL cholesterol (De Kleijn et al., 2002). In both studies a self-reported food questionnaire was completed by the participants from which the investigators determined the intake of the isoflavones, daidzein, genistein **2**, formononetin, biochanin A, and coumestrol **3** and the lignans, matairesinol **5** and secoisolariciresinol comprising the total phytoestrogen consumption level. In a prospective study by Vanharanta et al. (2003), the serum enterolactone concentration in middle-aged men was correlated with a decreased risk of CVD and CVD related mortality.

Although no clinical studies showed that resveratrol **4** improves cardiovascular function, the consumption of red wine has been linked to the French Paradox (Goldberg et al., 1995; Kopp, 1998; Ashby et al., 1999). This phenomenom is observed in French people who have a diet similar to the North American diet with a significantly lower rate of CVD (Kopp, 1998; Ashby et al., 1999).

10. Cognitive abilities

Many postmenopausal women feel that their cognitive abilities decline during menopause, and some believe that HRT may alleviate this decline. There is, however, no clear evidence to support this belief (Hogervorst et al., 2000). A few studies have examined the effect of phytoestrogens on cognitive function. A ten-week study demonstrated that diets high in soy increased student's long term and short-term memory. For this study, male and female students were assigned either a high (100 mg/day) or low (0.5 mg/day) isoflavone diet. At the beginning and end of the study period the subjects were tested for a variety of cognitive skills. The students in the high isoflavone diet group had significant improvements in short term and long term memory, and mental flexibility (File et al., 2001). The low isoflavone group had no change in these parameters. Since the low isoflavone diet was also low in soy products, it is unclear whether the phytoestrogens are responsible for this effect.

A follow-up study of the cognitive functions of postmenopausal women taking soy isoflavonoids or a placebo showed increase in recall of pictures, sustained attention, and ability to plan tasks (Duffy et al., 2003). These women did not demonstrate any improvement in menopausal symptoms, mood or sleepiness. This suggests a specific improvement in frontal lobe functions and the cognitive improvements were not the result of a better quality of life (Duffy et al., 2003).

11. Cancer

There is a large body of epidemiological studies showing people who consume high amounts of isoflavonoids in their diets have lower rates of several cancers including breast, prostate and colon cancer (American Institute for Cancer Research, 1997). In Asia, where consumption of phytoestrogens is high the rates of these cancers are low. Immigrants from Asia living in the US have an increased risk of cancer compared to people living in Asia. The increase in cancer rates is correlated with the length of stay in the US and the exposure to the North American diet (Ziegler et al., 1993; American Institute for Cancer Research, 1997).

A high plasma concentration of the mammalian lignan, enterlactone, is correlated with a reduced risk of breast cancer (Pietinen et al., 2001; Boccardo et al., 2004). The women in the quintile with the highest circulating enterolactone concentrations have half the risk of developing breast cancer than the lowest quintile (Pietinen et al., 2001). Similar correlations have been found between dietary intakes of isoflavonoids and lignans and thyroid (Horn-Ross et al., 2002a), ovarian (McCann et al., 2003), and breast (Lee et al., 1991; McCann et al., 2002) cancers in pre- and post-menopausal women. In contrast a large study that examined dietary factors and breast cancer following a cohort of 111,526 women in California, found no association between phytoestrogens and breast cancer (Horn-Ross et al., 2002b). A nested case control study in Finland found no correlation between serum enterolactone concentration and the risk of developing breast cancer in pre or post menopausal women (Kilkkinen et al., 2004).

Urinary excretion of phytoestrogen metabolites can be used as a biomarker for the intake and bioavailability of the phytoestrogens. Two retrospective studies that examined the excretion of phytoestrogens and the risk of developing breast cancer, showed a lower risk of breast cancer in women with increased excretion of phytoestrogens. A case control study that measured the urinary excretion of isoflavonoids and lignans found that breast cancer patients had significantly lower excretion of phytoestrogens than healthy subjects (Dai et al., 2002). A second report, that was part of a larger multiyear study, examined the excretion of the metabolites in urine collected from 1 to 9 years before patients developed breast cancer. This was compared with matched subjects that had not developed breast cancer (den Tonkelaar et al., 2001). There was a trend to a lower risk of developing breast cancer with higher excretion of isoflavonoids and lignans although this trend was non-significant (den Tonkelaar et al., 2001). A case control study conducted by Kilkkinen et al. (2003) examined the plasma enterolactone concentration in men and found no correlation with risk of prostate cancer.

The protective effect of phytoestrogens on cancer may be due to their role in lowering circulating levels of unconjugated sex hormones. Estrogens mainly circulate as inactive conjugates of sex hormone binding globulin (SHBG) or albumin (Dotsch et al., 2001). Dietary supplementation with soy isoflavonoids or lignans were shown to increase the levels of SHBG (Adlercreutz et al., 1992; Pino et al., 2000; Berrino et al., 2001; Hutchins et al., 2001), in postmenopausal women, lowering the serum levels of free estradiol **1** (Xu et al., 2000; Hutchins et al., 2001; Lu et al., 2001). In menstruating women the effect of phytoestrogens on estrogen levels is less clear as most supplementation studies found no difference in menstrual cycle length or hormone levels with soy supplementation (Nagata et al., 1998; Martini et al., 1999; Maskarinec et al., 2002; Nicholls et al., 2002). Higher ingestion of isoflavonoid and flaxseed produced a significant decrease of urinary excretion of genotoxic estrogen metabolites. Three major pathways, leading to different metabolites, can metabolize estradiol **1** and estrone. Two of these pathways produce 16α-hydroxyestrogens and 4-hydroxyestrogens, which are known to be genotoxic (Xu et al., 1998). The 2-hydroxyestrogen metabolites are proposed to exert a protective effect

towards breast cancer, and the ratio of 2-hydroxyestrogens to 16α- hydroxyestrogens is considered to be an important breast cancer biomarker (Haggans et al., 1999). The level of serum SHBG is negatively correlated with the urinary excretion of 16α hydroxyestrogens (Adlercreutz et al., 1992).

12. Menopausal symptoms—quality of life

Some women experience a decrease in the quality of life during menopause due to sleep deprivation, hot flashes, mood swings, forgetfulness and difficulty concentrating. These symptoms are linked to the declining and erratic production of estrogen by the ovaries. Doctors often recommend HRT for relief of these symptoms; however, a recent study by the Women's Health Initiative (Hays et al., 2003), found relatively few benefits of HRT for quality of life parameters. A subset of woman, 50–54 years of age with moderate to severe symptoms, had significant decreases in sleep disturbance and hot flashes; however, for all other symptoms and groups there was no clinically significant improvement (Hays et al., 2003).

With the lower than expected effectiveness of HRT, it is not surprising that few studies show a benefit in the reduction of menopause symptoms with phytoestrogen supplementation. Several studies showed a significant drop in the severity and frequency of menopausal symptoms compared with the beginning of the study. However women given placebos also demonstrated a decline in menopausal symptoms; therefore there was no significant difference between control and treated groups (Washburn et al., 1999; Kotsopoulos et al., 2000; Quella et al., 2000; Scambia et al., 2000; Carranza-Lira et al., 2001; Clifton-Bligh et al., 2001; Nikander et al., 2003; Tice et al., 2003). There is currently not enough clinical evidence demonstrating the effectiveness of phytoestrogens for the reduction of menopausal symptoms.

13. Concluding remarks

Diet and nutrition contribute to the different rates of cancer and other diseases throughout the world (American Institute for Cancer Research, 1997). Diets rich in plant-derived products may supply a variety of phytoestrogens capable of producing a range of pharmacological effects in the human body. As people live longer, women are spending more of their lives in menopause, affected by a variety of estrogen-related conditions such as osteoporosis, cognitive and cardiovascular decline, increased risk of breast cancer and other symptoms that decrease the overall quality of life. Unfortunately, HRT was found to be less effective in decreasing the severity of some of these conditions than previously thought and may actually increase the risk of cancer. Regrettably, the understanding of the potential health effects of phytoestrogens, plant-derived cousins of estradiol **1**, is also far from complete. Many factors contribute to this lack of understanding that exists despite the 105 clinical trials summarized in this review. For instance, the great diversity of phytoestrogens makes it difficult to make general conclusions about their health effects, since different members of this class may have different activities, pharmacokinetic properties and metabolic fate. Clinical trials that study phytoestrogens are often performed with a variety of botanical formulations and thus cannot be compared directly. Non-estrogenic compounds present in phytoestrogen-rich plant sources used in clinical research may interact with phytoestrogens and either potentiate or interfere with their activity and bioavailability. In addition, some phytoestrogens may act as estrogen agonists or antagonists depending on their structure and concentration. The above factors underscore the difficulties of studying the clinical effects of bioactive mixtures over the single-ingredient pharmaceuticals.

Because of the difficulties in studying the pharmacology of phytoestrogens present in foods, we still are not sure whether these foods change the risk of breast cancer, cardiovascular disease or cognitive decline in pre- and postmenopausal women. The strongest body of evidence supports the view that at least soy isoflavonoids may be effective in preventing osteoporosis, although their effect is probably weaker than that of HRT.

Clearly, much research is required to clearly define the pharmacological effect of dietary phytoestrogens. It is essential that future studies be performed with standardized and structurally characterized mixtures of compounds or with isolated phytoestrogens. An exciting prospect of the future phytoestrogen research lies in the separation of their effects from the action of human estrogens. For example, the fact that some phytoestrogens may differ from human estrogens in their affinity to the ERβ than to ERα or may function as estrogen agonists may provide the basis for separating the undesirable effects of estrogenic compounds on cell proliferation from their beneficial effects on bone density and general health. Thus, some dietary phytoestrogens may decrease menopausal symptoms without increasing the risk of breast cancer. This is just one of many opportunities that exist in the study of the endocrine effects of food components and in defining their pharmacological use.

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